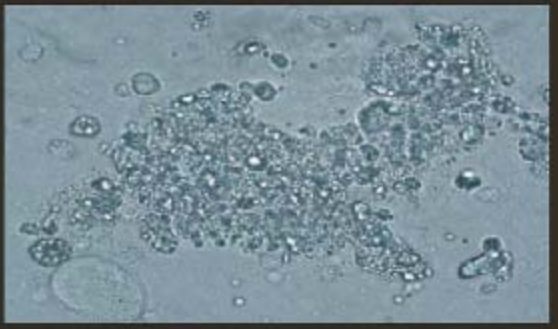
Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Edited by

Daniel A. Shoskes, MD



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Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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Edited by

Daniel A. Shoskes, MD
Glickman Urological and Kidney Institute, Cleveland Clinic,
Cleveland, Ohio

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Editor
Daniel A. Shoskes, MD
Glickman Urological and Kidney Institute
Cleveland Clinic, Cleveland, Ohio

Series Editor
Eric A. Klein, MD
Professor of Surgery
Cleveland Clinic Lerner College of Medicine
Head, Section of Urologic Oncology
Glickman Urological and Kidney Institute
Cleveland, OH

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Preface

Prostatitis is a clear enigma within urology; a group of conditions that is at once extremely common, poorly understood, inadequately treated, and under-researched. When I developed a research interest in the conditions about ten years ago, a careful read of the literature to date was quite surprising. The classification system was based upon the "4-glass test," which was designed to help localize bacterial infections and had never been validated for other use. There was no validated symptom score. There was not a single randomized placebo-controlled trial using symptoms as an outcome. The condition was clearly a "wastebasket of urology." When speaking at academic meetings, I seldom failed to get a laugh adding "…and I'm not the most junior member of the faculty" to my introduction.

Ten years later, much has changed. National Institutes of Health funding support has brought new investigators into the field. We now have a classification system based upon clinical syndromes rather than etiology (which is still unknown). Outcomes research has improved our understanding of the incidence, quality of life impact, and economic impact. We have a validated symptom score that appears to adequately measure both symptom severity and response to therapy. Randomized placebo-controlled trials are now the rule rather than the exception. Established dogma on the investigation, therapy and indeed the prostatic origin for many men with "chronic prostatitis" is being challenged.

The purpose of this book is to review the state of the art in prostatitis combining practical clinical recommendations with cutting-edge clinical research, basic science, and questions for the future. We have assembled a diverse international group of contributors that includes urologists (academic, primary care, and front-line private practice), scientists, psychologists, pain specialists, and directors from the National Institute of Health. Chapters cover general evaluation of the prostatitis patient; the approach to acute prostatitis; chronic bacterial prostatitis and chronic pelvic pain syndrome; evidence behind individual therapies; and ancillary topics such as erectile dysfunction, infertility, the link between chronic prostatitis and prostate cancer; male interstitial cystitis; and the potential etiologic role of calcifying nanoparticles. We conclude with reviews of where we have come from and where we may be going and a practical summary chapter of therapy for chronic pelvic pain syndrome based upon established data and clinical experience.

It is my sincere hope that readers can find novel approaches in this text to help their patients. I also hope that in another ten years, we will be able to marvel at how much more has been accomplished and how the suffering of men with prostatitis has been eased.

Daniel A. Shoskes, MD

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Contributors

Amgad Abdu, MD
Pain Management Center, The Cleveland Clinic,
Cleveland, OH

Jonathan Bergman, MD
Department of Urology,
David Geffen School of Medicine at UCLA,
Los Angeles, CA

Elizabeth A. Calhoun, PhD
University of Illinois at Chicago, Chicago, IL

Neva Ciftcioglu, PhD
Nanobac Pharmaceuticals, Inc,
Lyndon B. Johnson Space Center, Houston, TX

J. Quentin Clemens, MD
Northwestern University, Feinberg School of Medicine, Chicago, IL

Alain Duclos, MD
University of Montreal, St-Luc Hospital, Montréal, Québec,
Canada

Anna M.S. Duloy, BE
University of Illinois at Chicago, Chicago, IL

Russell Blair Egerdie, M.D., F.R.C.S. (C)
University of Western Ontario, St. Mary's General Hospital,
Urology Associates/Urologic Medical Research, Kitchener, Ontario, Canada

Lawrence S. Hakim, MD, FACS
Department of Urology, Cleveland Clinic Florida, Weston, FL

Jeffrey A. Jones, MD, MS, FACS, FACPM
Lyndon B. Johnson Space Center, Baylor College of Medicine, Houston, TX

J. Stephen Jones, MD
Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH

Jonathan D. Kaye, MD
Smith Institute for Urology, New Hyde Park, NY

John N. Krieger, MD
Harborview Medical Center, University of Washington, Seattle, WA

John W. Kusek, PhD
Division of Kidney, Urologic and Hematologic Diseases,
National Institute of Diabetes and Digestive and Kidney Diseases,
Bethesda, MD

Shaun Wen Huey Lee, PhD
University of Science Malaysia, Penang, Malaysia

Men Long Liong, MD
Lam Wah Ee Hospital, Penang, Malaysia,

Yee Vonne Liong
Lam Wah Ee Hospital, Penang, Malaysia

David McKay, PhD
Lyndon B. Johnson Space Center, Baylor College of Medicine,
Baylor Houston, TX

Nagy A. Mekhail, MD, PhD
Pain Management Center, Cleveland Clinic, Cleveland, OH

Robert Moldwin, MD
Interstitial Cystitis Treatment Center, Smith Institute for Urology
Long Island Jewish Health System, New Hyde Park, NY

Kurt G. Naber, MD, PhD
Urology Clinic, St. Elisabeth Hospital, Straubing, Germany

Samer Narouze, MD
Pain Management Center, The Cleveland Clinic, Cleveland, OH

Carvell T. Nguyen, MD, PhD
Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH

J. Curtis Nickel, MD
Department of Urology, Queen's University
Kingston, Ontario, Canada

Leroy M. Nyberg, Jr., PhD, MD
Division of Kidney, Urologic, and Hematologic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health, Bethesda, MD

Michel Pontari, MD
Temple University School of Medicine, Philadelphia, PA

Jeanette M. Potts, MD
Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH

Daniel A. Shoskes, MD
Glickman Urological and Kidney Institute,
Cleveland Clinic, Cleveland, OH

Dean A. Tripp, PhD
Departments of Psychology, Anesthesiology, Urology,
Queen's University, Kingston, Ontario, Canada

Florian M.E. Wagenlehner, MD, PhD
Clinic for Urology and Pediatric Urology, Justus-Liebig-University,
Giessen, Germany

Wolfgang Weidner, MD, PhD
Clinic for Urology and Pediatric Urology
Justus-Liebig-University, Giessen, Germany

Kah Hay Yuen, PhD
University of Science Malaysia, Malaysia

Scott I. Zeitlin, MD
Los Angeles Infertility and Prostatitis Medical Group, Los Angeles, CA

Chapter 1
Evaluation of the Prostatitis Patient

Carvell T. Nguyen and Daniel A. Shoskes

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Summary Category III chronic prostatitis (CP), or chronic pelvic pain syndrome (CPPS), is one of the most prevalent and morbid conditions in urology, and has significant impact on a patient's physical, mental, and even financial well-being. In the past, the evaluation and treatment of the man with CP/CPPS has been hindered by lack of knowledge regarding the etiology and pathogenesis of the syndrome. Moreover, the wide spectrum of clinical findings and lack of objective criteria in CPPS can make it difficult to identify a patient with the disease. However, through the collaborative efforts of many investigators and the National Institutes of Health, CPPS has become better understood, resulting in the development of evidence-based investigative procedures and therapies able to tackle the significant health problem posed by CP/CPPS. In this chapter, we will review the means by which a patient with suspected CP/CPPS can be efficiently and accurately evaluated, because misdiagnosis can lead to the omission or delay of potentially therapeutic interventions.

Keywords Chronic prostatitis; chronic pelvic pain syndrome; diagnosis; evaluation; imaging; studies.

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1 Introduction

Prostatitis, in all its forms, is one of the most common urological disorders and can affect men of any age. Approximately one-third of all men during their lifetime will experience symptoms consistent with prostatitis ***(1)***. Although often thought to be the result of bacterial infection, prostatitis may be characterized by inflammation without evidence of infection. In fact, fewer than 10% of cases of prostatitis are caused by bacteria ***(1)***. Category III prostatitis (CP), or chronic pelvic pain syndrome (CPPS) as it is now known, is the most common manifestation of the disease (accounting for 90% of cases) but remains the least understood.

The term CPPS represents the recent symptom-driven reclassification of the prostatitis syndromes and acknowledges that pain is the primary symptom of nonbacterial prostatitis (2). The new National Institutes of Health (NIH) classification scheme also recognizes our limited understanding of the etiology of the disease process and introduces the concept that other organs besides the prostate, such as the bladder or pelvic musculature, may contribute to the symptomatology of CP/CPPS.

The condition tends to strike younger men (median age of 43 years) and is characterized by perineal and genital pain, which can be unrelenting and physically as well as emotionally exhausting for patients. The impact of CP/CPPS on quality of life (QOL) for most patients cannot be underestimated; the Chronic Prostatitis Cohort (CPC) Study of 488 men diagnosed with CP/CPPS has confirmed that the QOL suffered by these patients is quite dismal and comparable with those suffering from Crohn's disease or undergoing chronic hemodialysis ***(3)***.

CP/CPPS is a considerable health problem in the United States, with an estimated prevalence between 2% and 16% and an estimated 2 million outpatient visits for prostatitis per year, exceeding those for benign prostatic hyperplasia (BPH) or prostate cancer ***(4–6)***. Studies have estimated that CP/CPPS constitutes 8–12% of visits to a urologist and 1–6% of visits to a primary care physician ***(7,8)***. Furthermore, the financial impact of CPPS is estimated at $4,400 per person-year in the United States, accounting for more than $2 billion a year in direct medical costs ***(9)***. Taken together, the data emphasize the significant burden of CP/CPPS upon the American health system.

However, CPPS is not limited to the United States and appears to have a global impact on men's health. Studies from Asia have revealed CPPS prevalence rates of 6%, 8.7%, and 2.7% in cohorts from Korea, Malaysia, and Singapore, respectively ***(10–12)***. Likewise, a Finnish study reported an incidence of prostatitis of 37.8 per 10,000 person-year whereas a validated Italian version of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) discovered that prostatitis represented 12.8% of all urology outpatient visits in Italy ***(13,14)***.

Given the wide prevalence and significant morbidity of CP/CPPS, it is of the utmost importance to identify patients with the syndrome so that proper treatment and counseling regimens can be instituted without delay. In this chapter, we will discuss the components of the workup for CP/CPPS and determine which of the myriad tests and studies available are the most effective in making the diagnosis.

2 Clinical Presentation

Pain is the most severe and commonly reported symptom in patients with CP/CPPS ***(15,16)***. The "classic" presentation is that of a patient who presents with pelvic, perineal, or genital pain associated with voiding and/or sexual dysfunction, characterized by a relapsing, remitting course. However, presentation can be extremely variable among patients with CP/CPPS, and the wide constellation of signs and symptoms associated with the syndrome (and which often overlap with other urological disorders) make it difficult to make the diagnosis with certainty. A systematic evaluation that will allow accurate and early diagnosis of CP/CPPS begins with a complete history and physical.

3 History

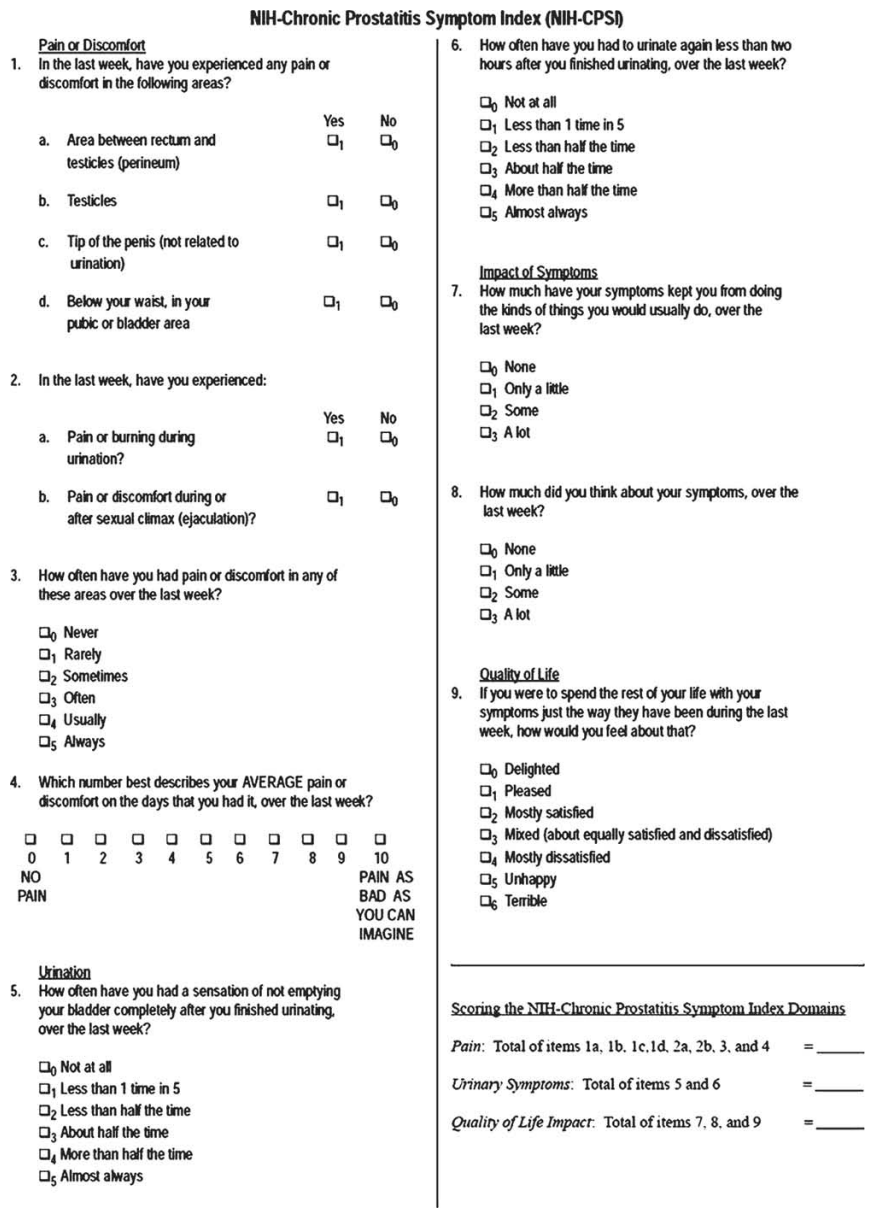
A complete and thorough history is a mandatory component of the workup for CP/CPPS and should assess the four cardinal symptom categories of CPPS (perineal/pelvic pain, voiding symptoms, sexual dysfunction, and systemic complaints) and their impact on a patient's quality of life.

Pain is the most common complaint of patients with CPPS and should be adequately characterized by the assessing the following:

Onset:	usually sudden.
Duration:	must be present for at least 3 of the last 6 months.
Intensity:	can be quite severe.
Location/radiation:	most often perineal and genital discomfort but can manifest itself in any of several regions, including lower abdomen (bladder), penis, scrotum, rectum, and lower back.
Course:	CPPS is notorious for a waxing and waning course with variable remissions and sudden flare-ups.

Irritative voiding symptoms such as dysuria, frequency, and urgency are likely to be reported by patients, Obstructive symptoms are less common but can include hesitancy, reduced flow, dribbling, or sensation of incomplete emptying.

A detailed sexual history is essential because sexually related complaints, such as ejaculatory pain, premature ejaculation, erectile dysfunction, or decreased libido, are quite prevalent in the CP/CPPS population and can provide diagnostic as well as prognostic information ***(17–19)***. In fact, postejaculatory pain is a specific symptom that may serve to distinguish prostatitis from BPH and may also portend a more severe disease course ***(20,21)***. Assessment of the frequency, quantity, and quality of ejaculation also can provide diagnostic information. For example, ejaculatory frequency often is reduced in CPPS patients because of pain or decreased libido, and ejaculatory volume and pressure also may be decreased. Furthermore, quality and appearance of the ejaculate may provide clues to associated pathology: yellow



NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a. Area between rectum and testicles (perineum)	☐1	☐0
b. Testicles	☐1	☐0
c. Tip of the penis (not related to urination)	☐1	☐0
d. Below your waist, in your pubic or bladder area	☐1	☐0

2. In the last week, have you experienced:

	Yes	No
a. Pain or burning during urination?	☐1	☐0
b. Pain or discomfort during or after sexual climax (ejaculation)?	☐1	☐0

3. How often have you had pain or discomfort in any of these areas over the last week?

☐0 Never
☐1 Rarely
☐2 Sometimes
☐3 Often
☐4 Usually
☐5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
0 1 2 3 4 5 6 7 8 9 10
NO PAIN — PAIN AS BAD AS YOU CAN IMAGINE

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

☐0 Not at all
☐1 Less than 1 time in 5
☐2 Less than half the time
☐3 About half the time
☐4 More than half the time
☐5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

☐0 Not at all
☐1 Less than 1 time in 5
☐2 Less than half the time
☐3 About half the time
☐4 More than half the time
☐5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

☐0 None
☐1 Only a little
☐2 Some
☐3 A lot

8. How much did you think about your symptoms, over the last week?

☐0 None
☐1 Only a little
☐2 Some
☐3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

☐0 Delighted
☐1 Pleased
☐2 Mostly satisfied
☐3 Mixed (about equally satisfied and dissatisfied)
☐4 Mostly dissatisfied
☐5 Unhappy
☐6 Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c,1d, 2a, 2b, 3, and 4 = _____

Urinary Symptoms: Total of items 5 and 6 = _____

Quality of Life Impact: Total of items 7, 8, and 9 = _____

Fig. 1 The NIH-CPSI questionnaire provides a validated outcome measure for men with CP/CPPS

color may indicate inflammation or infection whereas rust-stained ejaculate suggests hematospermia. Determination of any previous history of sexually transmitted diseases or urethritis is also important.

Systemic symptoms are not predominant in CP/CPPS but may include severe and chronic fatigue, arthralgias, myalgias, headache, somnolence, or painful

lymphadenopathy ***(19)***. Some patients may report an apparent predisposition to mild illnesses (such as the common cold) whereas others have demonstrated impaired memory, inability to concentrate, or depressive symptoms ***(22,23)***. Impact of disease on a patient's QOL is also a critical point to assess. It has been shown that the negative impact of the CP/CPPS on QOL is comparable with that of patients suffering from myocardial infarction or Crohn's disease ***(24)***.

The NIH Chronic Prostatitis Symptom Index (NIH-CPSI) questionnaire (Fig. 1), the first validated tool for assessing symptom severity in CP/CPPS, can be a useful in quantifying signs and symptoms and their impact on a patient's quality of life. Although designed primarily as a research tool in the follow-up of CP/CPPS ***(25)***, the CPSI has been used widely among practicing urologists for diagnostic purposes and has been translated and validated in several languages ***(26)***.

Additional elements of the history that are important include medical, surgical, and occupational/recreational history, medications, and any prior history of treatment directed at their CP/CPPS symptoms. History of urinary stone formation is important, as many of the symptoms of CPPS can be mimicked by a ureteral stone. When reviewing surgical history, particular attention should be paid to previous genitourinary procedures, such as herniorraphy, prostate/bladder surgery, or any endoscopy. Occupational and recreational history can be valuable in identifying sources of perineal stress, such as prolonged sitting or bicycle riding, which has been postulated to cause prostatitis ***(27)***.

4 Physical Examination

A focused physical examination will address all aspects of the genitourinary system, including the penis, scrotum, perineum, prostate, and peri-anal and inguinal areas. It is important to exclude other disorders such as inguinal hernia, nerve entrapment, or musculoskeletal inflammation because causes of pelvic pain that could be mistaken for that of CPPS. Suprapubic tenderness, a common physical finding in patients with interstitial cystitis (IC), may be elicited in some men presenting with CP/CPPS. There is a significant overlap of symptoms between IC and CPPS, with suprapubic tenderness, urinary frequency, and relief of pain after urination more common in men with IC ***(28)***.

The most critical component of the examination is the digital rectal examination (DRE), which should be used to assess the size, consistency, symmetry, and tenderness of the prostate. The majority of patients with CP/CPPS will have a completely normal prostate exam on DRE. Some patients, however, may present with any of the following: tenderness to palpation, boggy or indurated consistency, or crepitance. There is no evidence that a "boggy" prostate is diagnostic of prostatitis, however, and this finding in isolation appears to be of no significance. The internal pelvic musculature also should be palpated during a DRE to detect muscle trigger points that can elicit muscle spasm or pain. Interestingly, patients will often report that

their symptoms can be reproduced by palpation of these trigger points, some of which can be located far from the prostate.

As mentioned previously, a careful examination may reveal other conditions masquerading as CP/CPPS. For example, severe tenderness elicited by palpation of the pudendal nerve at the point where it dives under the sacrospinal ligament may be a sign of pudendal nerve entrapment, a rare condition that may mimic the symptoms of CP/CPPS ***(29,30)***.

5 Differential Diagnosis of CPPS

There are many urological and systemic diseases that have symptomatic manifestation in or around the prostate and may mimic CP/CPPS (Table 1). Patients with classic symptoms consistent with prostatitis may instead be diagnosed with bladder cancer, prostate cancer, varicocele, or, IC. A proper diagnostic workup for patients suspected of having CP/CPPS should be able to rule out these other conditions, some of which are potentially life-threatening.

5.1 Laboratory Studies

Although much research has been directed at the identification of laboratory markers that might correlate with the symptoms of CP/CPPS, we still lack definitive objective criteria for diagnosis of the disease. Conventional microbiological assays have failed

Table 1 Conditions that can mimic CP/CPPS

Granulomatous prostatitis
Various abscesses and cysts (e.g. utricle, Mullerian duct cyst)
Prostatic infections (tuberculosis, fungal)
BPH
Fistulae from adjacent organs
Prostatic urethral stricture
Varicocele
Seminal vesiculitis/obstruction
Bladder/prostatic calculi
Ureteral lithiasis
Tumors of the prostate (benign & malignant)
Urinary tract infection
Interstitial cystitis
Overactive bladder (detrusor instability)
Radiation cystitis
Bladder cancer
Urethral diverticulum
Bacterial urethritis
Diabetes mellitus
Pudendal nerve entrapment

to consistently detect any pathogenic organisms that may be responsible for CP/CPPS. However, laboratory studies can play an integral role in the workup of CP/CPPS by fully characterizing the type of chronic prostatitis as well as ruling out other pathology. Differentiating between urinary tract infection, chronic bacterial prostatitis, and chronic non-bacterial prostatitis (CPPS) depends on the presence or absence of bacteria in urine and expressed prostatic secretions (EPS), along with the clinical history. CP/CPPS, corresponding to category III in the NIH classification scheme, can be further divided into IIIA, representing an inflammatory subtype with leukocytes in semen, urine, or EPS, and IIIb, the noninflammatory subtype. There is no evidence, however, that the subtypes respond differently to therapy.

A urine analysis and culture should be performed on all patients being evaluated for CP/CPPS because positive findings (such as hematuria or bacteriuria) generally suggest diagnoses other than CPPS. Critical to the diagnosis of CPPS is the presumption that uropathogenic bacteria are not responsible for the pathogenesis or symptomatology of the syndrome. Generally, one will find an absence of uropathogenic bacteria on standard culture and, indeed, urine culture is negative in the majority of cases. However, not all cases of CP/CPPS will demonstrate sterility of the urine or prostate-specific samples. For example, a study by Lee and colleagues ***(31)*** found prostate biopsy cultures were positive for bacteria in 38% of men with CP/CPPS, but this rate was comparable to the 36% positivity rate among controls. There are data that suggest that cryptic pathogens, including *Chlamydia trachomatis, Mycoplasma hominis, Trichomonas vaginalis*, and various viruses (e.g., cytomegalovirus or herpes simplex virus), may contribute to the pathogenesis of CP/CPPS ***(32)***.

A lower urinary tract localization test, such as the Meares-Stamey 4-glass test or the pre- and post-massage 2-glass test (PPMT), is intended for the detection of prostate-specific inflammation and/or infection and is recommended at least once in the workup of CP/CPPS ***(26,33)***. The PPMT consists of analysis of urine samples taken before and after prostatic massage, whereas the 4-glass test, described by Meares and Stamey in 1968, consists of samples taken from the first 10 mL of urine (VB1), the mid-stream urine (VB2), the expressed prostatic secretion (EPS), and the first 10 mL of urine passed after prostatic massage (VB3). Greater levels of bacteria or leukocytes in the EPS or post-massage urine (VB3) compared with pre-massage urine are consistent with a diagnosis of prostatitis. Figure 2 demonstrates examples of findings in EPS, including leukocytes and corpora amylacea (Fig. 2A–C). It is important to note that the Meares-Stamey test was designed as a bacteriologic localizing study for men with documented infection, and its use in men without UTI (e.g., CPPS) has never been validated.

Controversy surrounds the value of localizing white cells and pathogens to prostatic secretions in the assessment of CP/CPPS. Although data from the CPC study demonstrate that almost 10% of patients test positive for established uropathogens on localization tests and that men with CP/CPPS have significantly greater white cell counts in all samples of a 4-glass test when compared with asymptomatic controls, leukocyte and bacterial counts do not seem to correlate to symptom severity, nor do they predict response to treatment ***(34–36)***. This confusing finding could be attributable

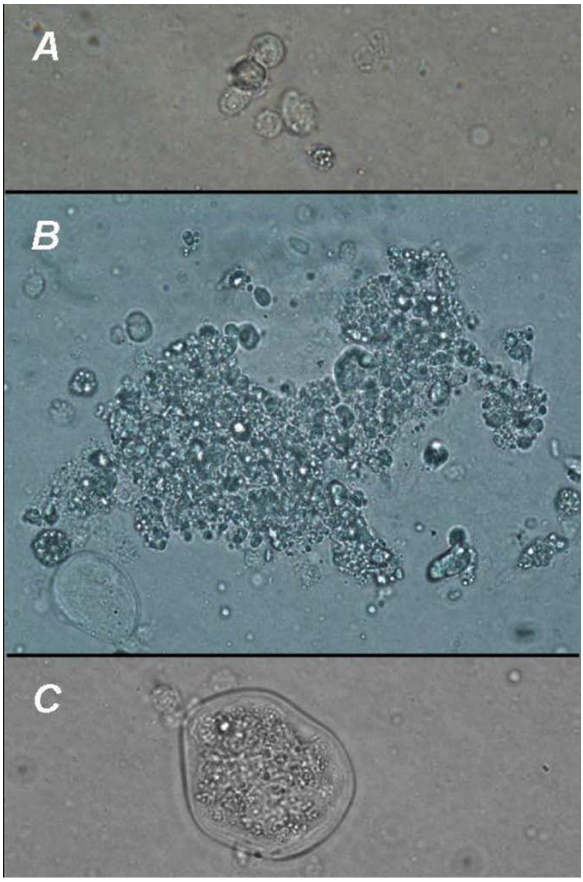


Fig. 2 Examples of wet mounts of expressed prostatic secretions (EPS) as seen under light microscopy. (A) Represents a leukocyte; (B) shows a clump of white cells that may have been extruded from a prostatic duct. Shown in (C) is an example of corpora amylacea, laminated luminal secretions that are commonly present in prostatic glands and thought to be related to epithelial cell desquamation and degeneration

to the observed lack of correlation between actual EPS white blood cell (WBC) concentrations and traditional WBC counts as determined by microscopy of gram-stained smears or wet mounts (which can be variable in their setup and interpretation) ***(37)***. It has been suggested that EPS WBC concentrations are most accurately determined by utilization of a counting chamber ***(37)***. Nevertheless, the added utility of using a counting chamber is not established and certainly not part of a patient evaluation outside of a research setting. Furthermore, a study conducted by the Chronic Prostatitis Collaborative Research network suggested that the 4-glass test was not able to distinguish men with CP/CPPS from asymptomatic controls as both groups exhibited high prevalence of leukocytes and positive bacterial cultures ***(35)***.

A recent report from the CPC study comparing PPMT to the Meares-Stamey 4-glass test found that the PPMT had strong concordance with the 4-glass test,

arriving at a correct diagnosis in greater than 96% of patients with CP/CPPS ***(38)***. Finding that presence of leukocytes or bacteria in VB3 (postmassage urine sample) could predict the presence of same in the EPS, the investigators suggested that the PPMT may be an acceptable (albeit, indirect) alternative to the 4-glass test in screening for prostate-specific bacteria and leukocytes in men with CP/CPPS. Combined with the observation that the 4-glass test is seldom used among urologists in practice because of its complicated, expensive, and time-consuming nature ***(39,40)***, it would be fair to recommend the use of the PPMT as an initial screening test in the workup of CP/CPPS ***(41)***. Lower urinary tract localization tests in general may demonstrate their greatest value in directing appropriate treatment in patients with a history of recurrent UTI or positive findings on urine culture ***(38)***.

There are several other laboratory tests that may serve a purpose in the workup of CPPS in select patients and clinical situations. Urine cytology, although not necessary in all men with CP/CPPS, should be considered in those patients presenting primarily with irritative symptoms or hematuria (microscopic and gross) in whom bladder malignancy is suspected, because the incidence of bladder CIS in this population is significant ***(42)***.

As mentioned previously, the vast majority of cultures in patients with CP/CPPS are negative. However, this finding may not be the result of an absolute absence of pathogenic microorganisms because some bacteria are resistant to conventional culture techniques. Detection of bacteria-specific DNA sequences with the polymerase-chain reaction (PCR) assays has been assessed as a possible adjunct in the detection of culture-resistant bacteria in CP/CPPS. A study by Riley and colleagues ***(43)*** demonstrated PCR positivity for bacteria-specific 16 s rRNA-encoding DNA (rDNA) in prostate tissue from 77% of CP/CPPS patients who had negative cultures. However, other investigators have data suggesting that presence of these bacterial rDNAs is not specific to CP/CPPS and can also be isolated from patients with prostate cancer ***(44)***. As such, PCR-based assays for bacterial rDNAs remain experimental but may hold promise if clinically validated.

Urethral swabs or rapid DNA PCR tests may be warranted in those with a history of urethral discharge or unprotected sex to rule out gonorrhea, chlamydia, or mycoplasma. The relevance of a co-existing sexually-transmitted disease to the pathogenesis of CPPS itself is currently unknown. Urethral swabs may also prove useful in distinguishing urethritis from prostatitis as data suggest that urethral smears are more sensitive in detecting urethral inflammation compared with analysis of VB1 or VB2 samples from a 4-glass test ***(45)***.

Similarly, semen analysis and culture are not routinely recommended and can be reserved for specific cases such as the infertile man presenting with symptoms of CPPS. Interestingly, there are data in the literature demonstrating that increased leukocyte counts in EPS or in semen itself do not negatively impact semen parameters (e.g., total sperm count, motility, or morphology) ***(46)*** Furthermore, although there are studies that show a correlation between CPPS and pathogenic infection of the semen (e.g., mycoplasmas and chlamydia), the relevance of such infection to the pathogenesis and symptomatology of CP/CPPS remains unclear ***(47,48)***.

Although serum levels of prostate-specific antigen can be elevated in prostatitis, it is not specific for the disease, and there is currently no indication for prostate-specific

antigen measurement as a routine investigation in the workup of CP/CPPS, unless there is suspicion of prostate cancer ***(49)***.

5.2 Imaging

Radiographic imaging of the pelvis, including ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI), does not have an established role in the conventional workup for CPPS but may be useful in ruling out other conditions that may be mistaken for CP/CPPS. Transrectal ultrasonography (TRUS) is a rapid, cheap, and low-risk (i.e., no contrast or radiation) imaging modality that assesses the prostate and surrounding structures, including the bladder, seminal vesicles, and ejaculatory ducts. Pathology, such as prostatic abscess, lithiasis, Mullerian cysts, or ejaculatory duct dilation, can be easily detected and potentially treated.

A small number of studies have reported on potential ultrasonographic findings such as detrusor and bladder neck thickness or volume of prostate hypoechogenicity that may be associated with CPPS ***(50,51)***. Prostatic lithiasis, in particular, is a common finding on TRUS and has long been linked to an inflammatory state within the prostate even though no etiologic relationship has been proven. A study from Greece, examining the relationship between prostatic lithiasis and CP/CPPS in a cohort of 1374 men who were screened with TRUS, discovered that the presence of large, coarse prostatic calculi correlated with chronic prostatitis symptoms ***(52)***. However, with no evidence for a causal relationship between lithiasis or other TRUS findings and CP/CPPS, the value of TRUS as a routine diagnostic tool in CPPS remains uncertain. Furthermore, some studies have shown no obvious ultrasonographic differences between CP/CPPS patients and controls ***(50)***.

A search of the literature reveals little data concerning the utility of CT scan in the diagnosis of CP/CPPS. Several studies have suggested that MRI, particularly endorectal, MR, can differentiate between malignant and benign conditions of the prostate and findings such as coarse calcifications or heterogeneity of the prostate may be markers of CP/CPPS ***(53–56)***. Other studies report that MRI is not sensitive enough to differentiate between various pathological conditions of the prostate ***(57,58)***. It appears that neither CT nor MRI can confirm a diagnosis of CP/CPPS but may be used if upper urinary tract pathology (such as nephrolithiasis or renal mass) is suspected.

5.3 Voiding Studies

Urine flowmetry and postvoid residual (PVR) determination by ultrasound can be useful in the investigation of men with CP/CPPS, particularly those in whom voiding symptoms predominate. Older data showed that patients with CP/CPPS demonstrated aberrant urine flowmetry parameters that distinguish them from normal controls ***(59)***. More recent studies suggest that abnormal findings on flowmetry

(e.g., decreased flow rates or increased PVRs) may orient the diagnosis towards other lower urinary tract conditions such as BPH ***(60)***.

Another controversial aspect of the diagnostic evaluation for CP/CPPS is whether urodynamics should be routinely performed. Some studies have suggested that there is a urodynamic profile specific for CP/CPPS that is characterized by functional obstruction at the level of the bladder neck, with the conclusion that the urodynamic abnormalities contribute to the pathogenesis of CP/CPPS ***(61,62)***. Other investigators support the stance that the utility of urodynamics is in excluding etiologies of complex voiding dysfunction that are independent of CP/CPPS ***(63–66)***. For example, urodynamic studies can identify patients misdiagnosed as CP/CPPS who instead suffer from bladder outlet obstruction (caused by BPH or bladder neck hypertrophy) or detrusor sphincter dyssynergia ***(63,64,67)***.

On the basis of these data, the greatest value of voiding studies seems to be their ability to rule out anatomic and functional causes of voiding dysfunction that are independent of CP/CPPS. Given the more complicated, expensive, and invasive nature of urodynamic testing, urine flowmetry and PVR determination is the simpler and perhaps better screening choice in the initial evaluation of CP/CPPS.

5.4 Endoscopy

Although not a routine investigation in the workup of CPPS, cystoscopy can reveal pathological changes in the urinary tract that may contribute to symptoms, such as urethritis or a diverticulum. It should be kept in mind that the invasive nature of cystoscopy could exacerbate any irritative process in the prostate or urinary tract, thereby worsening symptoms. Therefore, cystoscopy should be performed judiciously and can generally be limited to patients who present with hematuria, have positive cytologic findings, have abnormal urine flowmetry/PVR, or exhibit predominantly voiding symptoms (for which bladder neck pathology should be excluded). Pathology of the urinary tract, such as BPH, bladder tumors, or urethral stricture, can then be identified and treated.

5.5 Miscellaneous Investigations

5.5.1 Potassium Sensitivity Test

Intravesical instillation of potassium chloride may cause pain in patients with the symptoms of IC, which might represent underlying epithelial dysfunction (i.e., increased urothelial permeability) of the bladder in this patient population. As such, the potassium-sensitivity test (PST) has been used in some centers as a diagnostic tool in IC. An uncontrolled study by Parsons and Albo ***(68)*** showed PST positivity

in 84% men with CP/CPPS. A follow-up study by the same investigators using a control group confirmed the high rate of PST positivity in patients with prostatitis ***(69)***. However, a study by Yilmaz and colleagues ***(70)*** did not show a significantly greater rate of PST positivity in men with CP/CPPS when compared with normal men. Until more definitive data on the predictive value of the PST is available, we do not recommend routine use of this test in the evaluation of CP/CPPS.

5.5.2 Hydrodistention

Hydrodistention (HD) historically has been used as a diagnostic and therapeutic tool in patients with IC and, as with PST, has been evaluated for use in the context of CP/CPPS. Unfortunately, the data regarding the applicability of HD in CP/CPPS are conflicting. A study from the University of Washington revealed that 60% of patients with CP/CPPS were positive for petechial hemorrhages after HD ***(71)***. The authors concluded that a subset of men diagnosed with CP/CPPS may actually have, I. C. Conversely, Cole and colleagues ***(72)*** found no statistically significant differences in post-HD objective findings, including anesthetic capacity and glomerulations, or therapeutic benefits between patients who were divided into symptomatic groups corresponding to IC and CP/CPPS. Currently, there is not sufficient evidence to warrant inclusion of HD in the routine evaluation of CP/CPPS.

6 Conclusion

On the basis of our personal clinical experience and extensive review of the data in the literature, the optimal diagnostic workup for CP/CPPS should include the studies listed in Table 2. The tests shown in Table 3 are optional and may have utility in select patients and clinical situations and need not be performed in all patients.

Table 2 The Standard Evaluation for CP/CPPS

History (in conjunction with NIH CPSI)
Physical (with emphasis on DRE and pelvic floor evaluation)
Urinalysis/urine culture
Lower urinary tract localization test (PPMT or 4-glass test)
Uroflowmetry and PVR

Table 3 Optional Studies in the Evaluation of CP/CPPS

Urine cytology
PSA
Semen analysis
Cultures and swabs for STD
Pelvic imaging (TRUS, CT, MRI)
Urodynamics
Cystoscopy with or without hydrodistention

Clearly, there will be differences between patients who present initially and those with a long history of continuous or intermittent symptoms.

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Chapter 2
Acute Bacterial Prostatitis

Kurt G. Naber, Florian M. E. Wagenlehner, and Wolfgang Weidner

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Summary Acute bacterial prostatitis (NIH category I) is diagnosed clinically and from urine culture. It can be a serious infection, usually caused by uropathogens, with intense local pain, fever and other systemic symptoms. Prostatic massage is contraindicated, microbiological diagnosis is usually performed by the midstream urine.

Antimicrobial therapy is the most essential part of the therapeutic regimen. Treatment varies according to the severity of the patient's presenting symptoms and the probable etiologic agent. Antimicrobial treatment should be initiated immediately in patients with acute bacterial prostatitis after blood and urine cultures have been obtained. Initially, parenteral administration of high doses of bactericidal antibiotics, such as a broad-spectrum penicillin derivative, a third-generation cephalosporin with or without an aminoglycoside, or a fluoroquinolone, are required until fever and other signs and symptoms of infection subside. After initial improvement, a switch to an oral regimen, a fluoroquinolone, is appropriate and should be prescribed for at least 4 weeks. In less severe cases, a fluoroquinolone may be given orally for 2 to 4 weeks.

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Complications are nowadays rare and can be managed with minimal invasiveness in most cases. Special etiology and patient groups, such as HIV-infected patients however pose difficulties in diagnosis and treatment. It appears that rapid restoration of the immune status by highly active antiretroviral therapy is of paramount importance in these patients.

Keywords Acute prostatitis, urinary tract infection, antibiotics.

1 Introduction

Acute bacterial prostatitis (National Institutes of Health category I) is a well-described entity that is diagnosed clinically and from urine culture. Acute bacterial prostatitis frequently is a serious infection, usually caused by uropathogens and with intense local pain, fever, and other systemic symptoms, in which antimicrobial therapy is a most essential part of the therapeutic regimen. Acute prostatitis can potentially lead to urosepsis.

2 Epidemiology

There are no solid data on the prevalence and incidence of acute bacterial prostatitis. As a single entity, acute bacterial prostatitis is probably rare. However, acute urinary tract infections in males might also acutely involve the prostate in an unknown percentage ***(1,2)***. Incorporation of more sensitive laboratory methods for the diagnosis of acute bacterial prostatitis should be incorporated to investigate these data.

Milan et al. ***(3)*** described two different entities of acute bacterial prostatitis, depending on the patients history: spontaneous acute bacterial prostatitis and manipulated acute bacterial prostatitis. They retrospectively evaluated 614 patients with a diagnosis of acute bacterial prostatitis; 10% of the cases were elicited by urethral manipulation) and showed a different pattern from those cases in which no previous manipulation had occurred. The patients with acute bacterial prostatitis secondary to manipulation were older and had a greater risk of prostate abscess, greater frequency of multiple infections, and greater risk of infections by pathogens other than *Escherichia coli*, such as Pseudomonas spp. A total of 15.8% of all the patients with a diagnosis of acute prostatitis were admitted to the hospital. The most common complications were acute urinary retention (9.7%) and prostatic abscess (2.7%). The mean treatment time was 21 days, and in 12.7% of these patients the infection recurred. The mean treatment time among those who recurred and those who did not was statistically not different. Significantly more (31.5%) of the patients with a previous history of urinary tract manipulation recurred versus patients with no previous history (9%).

Only 14.3% of the patients required deobstructive surgery after their episode of acute prostatitis. This is one of the largest series on patients with acute bacterial prostatitis reported in the literature. The two different entities reported might be of particular interest, especially as the number of prostate biopsies for suspicion of cancer is increasing.

3 Pathogenesis

3.1 Microbiological Factors

The bacterial spectrum of acute bacterial prostatitis resembles that of complicated urinary tract infections. Cho et al. ***(4)*** performed a review of 255 inpatients with acute bacterial prostatitis from 10 hospitals. *E. coli* was isolated in 67%, *Pseudomonas aeruginosa* in 13%, *Klebsiella* sp. in 6%, and Gram-positive species in 5%.

In an experimental study, Rippere-Lampe et al. ***(5)*** found that infection of rat prostates with cytotoxic necrotizing factor type 1-positive uropathogenic *E. coli* caused more inflammation-mediated morphological and histological tissue damage than did infection with negative mutants. Ruiz et al (***6***) analyzed differences in the presence of other urovirulence factors among 111 clinical isolates of *E. coli* causing cystitis and pyelonephritis in women and prostatitis in men. Hemolysin, necrotizing factor type 1, the papGIII gene, aerobactin, and PapC occurred significantly more in prostatitis isolates compared with cystitis or pyelonephritis. The authors concluded that bacterial strains causing acute prostatitis need more virulence factors to cause prostatitis than for other urinary tract infections (UTIs). The same group ***(7)*** subsequently analyzed various virulence factors of, *E. coli* strains causing acute bacterial prostatitis. A total of 151 *E. coli* strains collected from patients with cystitis (44 strains), pyelonephritis (75 strains), and prostatitis (32 strains) were analyzed for in vitro biofilm formation, the phylogenetic group, the presence of several urovirulence factors and resistance to nalidixic acid. *E. coli* strains causing prostatitis produced biofilm in vitro more frequently than those causing other urinary tract infection.

3.2 Immunology

Nickel et al. ***(8)*** investigated a rat model of experimental bacterial prostatitis and examined the microbiological, histological, and immunological consequences of acute and chronic bacterial prostatitis. In the acute response, histopathological examination demonstrated severe infiltration of polymorphonuclear cells into the bacteria-containing ducts. An immunologic response could not be demonstrated in the acute phase of the infection.

Elkahwaji et al. ***(9)*** developed a reproducible mouse model of acute bacterial prostatitis to study the etiology and host factors associated with infection susceptibility. The group used male BALB/c, C3H/HeJ, C3H/HeOuJ, C57BL/6 J, and (BALB/c × C3H/HeJ)F1 mice and inoculated intraurethrally 10^6 to 10^8 *E. coli*. Significant bladder and prostate infections were not present in the BALB/c, C57BL/6 J, or (BALB/c × C3H/HeJ)F1 mice; however, C3H/HeJ and C3H/HeOuJ mice developed severe, acute bacterial prostatitis. The authors concluded that strain-dependent differences in susceptibility indicate that genetic factors may play a major role in the etiology of bacterial prostatitis. They speculate that infection susceptibility is a recessive trait, because F1 mice did not develop significant bladder and prostate infections, similar to the BALB/c parents. Gatti et al. ***(10)*** investigated how prostate epithelial cells deal with inflammatory stimuli. The group could demonstrate that prostate epithelial cells constitutively express significant levels of Toll-like receptor (TLR) 4, CD14, and Toll-like receptor 2 mRNA. TLR4, TLR2, and CD14 proteins also were detected, although not at the cell surface but intracellularly. The authors found out that prostate epithelial cells not only express these receptors but are also able to respond to lipopolysaccharide by activating nuclear factor-kappaB, by inducing the expression of inducible nitric oxide synthase, and by secreting nitric oxide. In this response, numerous chemokine genes are up-regulated or induced. This study demonstrated that the prostate epithelial cells are part of the innate immune system, capable of initiating an inflammatory response.

In another study, it was found that surfactant protein D, which is involved in host defense mechanisms in the lung, is also produced in epithelial cells of the human prostate, where it may play a role in innate immunity ***(11)***. Prostate glands that were surrounded by inflammatory cells produced increased amounts of surfactant protein, D. The authors could also show in an in vitro infection assay that surfactant protein D was able to inhibit the infection by *Chlamydia trachomatis* by binding to *Chlamydia trachomatis* via the carboxy-terminal lectin domains.

Ceri et al. ***(12)*** investigated the mucosal immunity in the rat prostate by stimulating the mucosal system through exposure of formalin-killed, *E. coli*. They found out that immunized rats developed bacterial-specific IgG and IgA in prostatic fluid, and IgA in urine, but not sham-immunized rats. Immunized and sham-immunized control rats were challenged by transurethral injection of, *E. coli* into the prostate ducts. Increased, *E. coli*-specific immunoglobulin titers were seen in immunized rats, as well as IgG- and IgA-coated, *E. coli*. They also found that immunization protected against toxemia and septicemia but did not protect against acute prostatitis nor alter the degree of tissue damage observed ***(12)***.

Kaplan et al. investigated in an early study the role of hormones in acute bacterial prostatitis ***(13)***. The group inoculated, *E. coli* into rat prostates and found positive bacterial cultures in the expressed fluid of the rat prostate for a prolonged period of time. Interestingly, the group found out that orchiectomy at the time of bacterial inoculation significantly shortened the interval of positive bacterial cultures in the prostate fluid.

4 Evaluation

The evaluation of patients encompass the clinical evaluation, laboratory investigations of blood and urine, and imaging. Application of methods such as scintigraphy, transrectal ultrasonography (TRUS), and serum prostate-specific antigen (PSA) may further assist in the diagnosis of acute bacterial prostatitis in addition to the physical examination and urine culture for patients with ambiguous pyrexia.

4.1 Clinical Evaluation

Patients with acute bacterial prostatitis usually complain of dysuria, urinary retention, or lower abdominal pain. "Panurogenital" infection (e.g., prostatitis, epididymitis, cystitis, pyelonephritis) may be found in combination in some patients. The patients frequently present with high-grade fever as a strong indicator of systemic infection. A complete urological, physical examination should be performed, comprising palpation of the costovertebral angle, abdomen, bladder region, testicles, and epididydimes and a gentle investigation of the prostate. The prostate usually appears tender and swollen. Accompanying epididymitis and orchitis results in painful enlarged testicles. Painful bladder region could be caused by severe cystitis or more often by urinary retention. The costovertebral angle should be painful to palpation if pyelonephritis is present.

4.2 Urine Analysis and Culture

Urine culture is considered the only laboratory evaluation of the lower urinary tract that is required. A midstream urine specimen will show significant leukocytosis and bacteriuria microscopically. Culturing usually shows typical uropathogens. For proper management, an immediate investigation leading to immediate treatment should be performed. Microscopic detection of leucocytes and bacteria in the Gram-stain or other methods of immediate urinalysis should therefore be implemented. Prostatic massage is contraindicated.

A comparative, controlled study evaluated the utility of urinary alpha 1-microglobulin, alpha 2-macroglobulin, and albumin in the diagnosis of acute prostatitis in 133 men and a reference population with cystitis, pyelonephritis, or without urinary tract infection ***(14)***. The urinary alpha 2-macroglobulin/albumin ratio was significantly lower in the population with prostatitis compared with the reference, cystitis, or acute pyelonephritis populations. Low alpha 2-macroglobulin concentrations in prostatitis are caused by inhibition of the immune reaction between alpha 2-macroglobulin in presence of polyclonal rabbit antibodies by soluble prostatic proteins that appear in urine in acute prostatitis. The authors concluded that the combination

of hematuria and the absence of urinary alpha 2-macroglobulin is diagnostic for acute prostatitis.

4.3 Imaging

Horcjada et al. ***(15)*** prospectively evaluated 45 patients with a clinical diagnosis of acute bacterial prostatitis with transrectal ultrasound. TRUS was performed upon admission and at 1 month after antibiotic therapy; findings correlated with clinical presentation and evolution of disease. The authors conclude that TRUS does not need to be performed on every patient with suspected acute bacterial prostatitis for diagnosis because only 47% had sonographically demonstrable lesions on admission and 61% had lesions that improved or disappeared after treatment. TRUS would be indicated in acute bacterial prostatitis to exclude the presence of prostatic abscess. Additionally, they concluded that ultrasound of the bladder should be performed to assess the degree of residual urine.

Mateos et al. ***(16)*** investigated 10 male patients with prostatitis and compared them with 6 men with UTI but without prostatitis to determine whether ^{111}indium-labeled leukocytes accumulated in the infected tissue and if uptake responded to treatment. Urinary and blood cultures also were conducted. Scintigraphs taken before antibiotic treatment showed uptake in prostates of all patients with acute bacterial prostatitis; after treatment, no uptake was noted in 9 of 10, and 1 of 10 had markedly decreased uptake. No uptake occurred in prostates of patients with UTI. ^{111}Indium-labeled leukocytes could be useful in detecting acute bacterial prostatitis, especially in clinically ambiguous patients with urological infections.

4.4 Laboratory Investigations

4.4.1 Serum Parameters

Serum parameters indicative for systemic infection should be investigated, such as leucocytes and C-reactive protein, to assess the degree of systemic infection. These parameters should also be reevaluated to determine the response to treatment.

4.4.2 Serum PSA

In a prospective study of 39 men with pyrexia (>38.3 °C), serum PSA levels were used to categorize patients according to an initial diagnosis of acute bacterial prostatitis, pyelonephritis, urogenital infection or fever of unknown origin (17). All of the 20 cases with pyrexia and elevated PSA were diagnosed and treated as acute bacterial prostatitis; treatment with antibiotics resulted in significantly reduced

serum PSA, fever, and normalization of C-reactive protein. The authors recommend PSA as a concise, accurate, rapid, and cost-effective tool for identifying acute bacterial prostatitis.

5 Treatment

Treatment of acute bacterial prostatitis varies according to the severity of the patient's presenting symptoms and the probable etiologic agent. Antimicrobial treatment should be initiated immediately in patients with acute bacterial prostatitis after blood and urine cultures have been obtained. Prostatic massage is contraindicated.

5.1 Antimicrobial Treatment of Acute Prostatitis

For effective antimicrobial therapy the pathogens at the site of infection must be exposed to a drug concentration sufficiently high to inhibit bacterial growth or even eradicate the pathogens from that site. There are substantial anatomic barriers to the passage of antibiotics from the circulation into the prostatic tissue and fluid ***(18)***. Most capillary beds are fenestrated and allow the passage of antimicrobial agents into tissue fluids fairly readily. There are several sites in the body in which nonfenestrated capillary beds pose barriers to the diffusion of antibiotics. The prostate gland is one of those sites, in conjunction with the central nervous system and the eye. Only lipid-soluble drugs traverse these capillaries readily. Additionally, pH partition may cause mean concentrations in the prostatic secretions to differ from those in the plasma at equilibrium.

The presence of a blood–prostate barrier was further substantiated by an experimental study in rats ***(19)***. The blood–prostate barrier is also not affected by lipopolysaccharide-induced acute inflammation. This barrier is persistent and apparently restricts the passage of leukocytes into prostatic secretion, even in the presence of pronounced interstitial inflammation.

Usually, pharmacokinetic barriers should be increased with the presence of severe acute inflammation; however, these experimental data for prostate are scarce. In one study the concentrations of cefminox sodium in serum and prostatic tissue were determined in 36 cases of prostatic hyperplasia with and without inflammation ***(20)***. Mean ratios of cefminox sodium in tissue over concentration in serum were 0.11 for patients with inflammation and 0.09 for those without inflammation and not significantly different.

Despite these experimental findings, the pharmacologic penetration of antibiotics in the acutely inflamed prostatic tissue is considered to be sufficient in the case of susceptible bacteria. At least in comparison with chronic bacterial prostatitis, where the choice of the ideal antibiotic substance is critical for clinical cure, in acute bacterial prostatitis a variety of antibiotic substances can be selected for initial treatment, all

with generally favorable clinical outcomes. Initially, parenteral administration of high doses of bactericidal antibiotics, such as a broad-spectrum penicillin derivative, a third-generation cephalosporin with or without aminoglycosides, or a fluoroquinolone, is required until fever and other signs and symptoms of infection subside. After initial improvement, a switch to an oral regimen, such as a fluoroquinolone, is appropriate and should be prescribed for at least 4 weeks ***(21)***.

5.2 Treatment of Prostatic Abscess

A prostatic abscess may require drainage in addition to antimicrobial treatment. Occasionally, anaerobes or mixed infections may be responsible for the abscess. Cultures should always be obtained. Most treatment regimens should include an agent effective against anaerobes. Prostatic abscesses can be drained through the urethra by transurethral resection of the prostate (TURP), the perineum by aspiration and through the rectum also by aspiration.

Chou ***(22)*** analyzed TRUS and color Doppler ultrasonography findings and therapeutic strategies with TRUS-guided procedures in 13 patients with prostatic abscess. The patients were treated conservatively if the abscess cavities were smaller than 1 cm in diameter; if not, the abscesses were drained by single aspiration or continuous draining procedures if cavities were larger than 1 cm in diameter. Abscesses with poorly defined boundaries had more prominent surrounding color-flow signals and the aspiration procedure was more difficult to perform in these cases. Single-procedure aspiration was done for all abscesses between 1 and 3 cm. Larger abscesses (>3.0 cm) were treated with aspiration using an 18-gauge needle or drainage using a 5-French pigtail catheter. The authors did not need to perform surgical drainage in all the patients.

Liu et al. ***(23)*** reviewed 17 cases of prostatic abscess. Most of the patients had either diabetes mellitus or hepatic cirrhosis. *K. pneumoniae* was the predominant pathogen of prostatic abscess and was frequently identified as the causative pathogen in patients with diabetes mellitus. Optimal management includes adequate drainage of abscess and antimicrobial therapy.

Maksimov ***(24)*** reported on thin needle transcutaneous puncture and drainage using a polyethylene catheter in 15 patients with prostatic abscess. The manipulation was well tolerated by all the patients with no complications in the postoperative period, and mean time of the abscess cavity draining was 4 days. A follow-up for 1.5 years discovered recurrence in none of the patients.

Collado ***(25)*** reviewed the management of 31 patients with prostatic abscesses. Ultrasound-guided needle aspiration resolved 83.3% of cases, and two patients needed to undergo a second procedure. Three patients required TURP for drainage and two to remove an obstruction after abscess resolution. The authors concluded that transrectal ultrasound-guided needle aspiration is a technically simple and effective therapeutic procedure with no morbidity and, in case of failure, may be repeated or a drainage TURP may be undertaken.

Ludwig *(26)* analyzed the findings and therapeutic strategies in 18 men with prostatic abscesses. Predisposing factors were important in the pathogenesis of prostatic abscess. The authors concluded that both operative and conservative therapy strategies appear feasible; however, drainage procedures should be individually selected.

5.3 Treatment of Urinary Retention

Alpha-receptors are present in the prostate, bladder neck, and central nervous system. Alpha-blockers have been demonstrated to improve bladder outlet obstruction and, therefore, alpha-blocker therapy has been advocated as a treatment modality for acute bacterial prostatitis. It has been suggested that α-blockers ameliorate the severe obstructive voiding symptoms associated with acute bacterial prostatitis *(27)*. However, this claim has not been substantiated by adequate clinical studies.

Acute urinary retention may be present in approximately 10% of patients *(28)*. Acute urinary retention in acute prostatitis can be managed by suprapubic, intermittent, or indwelling catheterization. Suprapubic tube placement is generally recommended because of theoretical reasons: it is believed that the fact that the veromontanum is not blocked by a urethral catheter would reduce the risk of prostatic abscess and urethral stricture, although this theory has never been substantiated by studies. Additionally, the accompanying bladder infection can cause severe irritative symptoms, which might result in a reduced bladder capacity rendering the insertion of a suprapubic catheter difficult. Many urologists therefore adopt either a single catheterization with a trial of voiding or short-term small caliber urethral catheterization. A retrospective series *(29)* suggested that urethral stenting may provide the same benefits of suprapubic catheterization.

5.4 Unusual Infections of the Prostate

5.4.1 Tuberculosis

Tuberculosis of the genitourinary system is the second-common form of extrapulmonary tuberculosis. Current reports on genitourinary tuberculosis are increasing *(29)*. Alongside with the growth of migration of the population and propagation of AIDS, which is a marker of genitourinary tuberculosis *(30)*, other important sources are Bacillus Calmette-Guerin (i.e., BCG) therapy for bladder cancer and kidney transplantation.

Kulchavenya *(30)* studied 514 patients with genitourinary tuberculosis; 414 had kidney tuberculosis only and 100 had genital involvement. Forty-two had tuberculosis of scrotal organs, and 58 had tuberculosis of the prostate. A total of 33.6% of all

patients earlier suffered from pulmonary or extrapulmonary tuberculosis and were successfully cured. In 61.9%, nephrotuberculosis was diagnosed alongside with an orchiepididymitis. In 30.9% of patients, bilateral epididymorchitis was diagnosed. Scrotal fistula were found in 11.9%. In 66.7%, the symptoms appeared acutely. Half of the patients with prostate tuberculosis complained of dysuria, 39.6% had perineal pain, and 58.6% had flank pain. Leucocytes in urine were present in 84.5% patients and in prostatic secretions in 77.6% patients. Erythrocytes in urine were present in 53,4% patients and in prostatic secretions in 29.3% patients.

Diagnosis of tuberculosis of the prostate is based on culture studies of urine or tissue, or histopathological examination of prostatic tissue ***(31)***. In one case report, Nakao et al. ***(32)*** reported on the use of transrectal biopsies and culturing of mycobacteria in the expressed prostatic expression. Reports on treatment strategies in patients with tuberculosis of the prostate are scarce. Drug treatment is the first-line therapy of prostate tuberculosis, which follows the therapeutic rules of urogenital tuberculosis in general. According to the World Health Organization, the anti-tuberculous drug treatment is based on an initial 2-month intensive phase of treatment with three or four drugs daily rifampicin, isoniazid, pyrazinamide, and ethambutol (or streptomycin) to destroy almost all tubercle bacilli ***(31)***. This is followed by a 4-month continuation phase with only two drugs mostly rifampicin and isoniazid. Only in complicated cases (recurrences of tuberculosis, immunosuppression and HIV/AIDS) a 9- to 12-month therapy is necessary. In cases with multidrug-resistant tubercle bacilli (bacilli resistant to rifampicin and isoniazid, with or without resistance to other drugs) therapy requires the use of at least four drugs that are selected on the basis of a drug susceptibility test (ethionamide, prothionamide, quinolones, clarithromycin, cycloserin, kanamycin, viomycin, capreomycin, thiaacetazone, and para-amino-salicide acid). The duration of therapy is based on the bacteriologic response but may be 18 months or longer.

Mycobacterium bovis is intrinsically resistant to pyrazinamide and is found in a high percentage of genitourinary tuberculosis. Pyrazinamide should be avoided in those cases also because of the induction of hyperuricemia and hyperuricuria. Treatment regimens of 6 months are effective in most patients. Nevertheless, in those patients with recurrences, tissue ablative treatment, either TURP or radical prostatectomy, may be required. Surgery should be performed not before the first 2 months of intensive chemotherapy ***(31)***.

5.4.2 Patients With HIV

Leport ***(33)*** evaluated the prevalence of bacterial prostatitis in 209 patients infected with the human immunodeficiency virus. Bacterial prostatitis was diagnosed in 8% of men with HIV. The prevalence of bacterial prostatitis among HIV-infected patients, however, increased from 3% in asymptomatic patients to 14% in patients with AIDS. Prostatic abscess was found in 70% of patients with prostatitis. Within

6 weeks after onset of antimicrobial therapy, 9 of 13 patients were cured; 4 did not respond to therapy. Among the seven patients followed for more than 2 months after the end of antimicrobial therapy, five relapsed. This study shows that acute prostatitis is a difficult to treat disease in these patients.

Trauzzi et al. ***(34)*** reviewed the management of prostatic abscess in seven patients with HIV. All patients presented with fever and irritative voiding symptoms; however, only one patient had a positive initial urine culture and three of five operative cases only had positive intraoperative culture. The organisms cultured were *Staphylococcus aureus*, enterococcus spp., *Mycobacterium tuberculosis*, and *Mycobacterium avium*. The authors concluded that TRUS is the imaging modality of choice for diagnosing this condition, and transurethral unroofing should be attempted whenever significant extension outside the prostate is not found. Because of the variable etiology intraoperative cultures for aerobes, anaerobes, fungi, and mycobacteria must be obtained.

Phillips et al. described the incidence and management of nontuberculous mycobacterial immune reconstitution syndrome in patients with HIV ***(35)***. The incidence of nontuberculous mycobacterial immune reconstitution syndrome was 3.5% among patients with a baseline CD4+ cell count of <100 cells/μL. The main clinical presentations in 51 patients were peripheral lymphadenitis, pulmonary-thoracic disease, and intraabdominal disease. Involvement of the prostate was rare and found only in 1 of 51 cases. The authors suggest that the main cornerstone of therapy is initiation of and adherence to highly active antiretroviral therapy (i.e., HAART). Prednisone was also associated with clinical response in eight of nine evaluable patients. The role of antimycobacterial therapy is uncertain, given the self-limited course of most nonabdominal cases ***(35)***.

Human herpesvirus-8 (HHV-8) DNA has been detected in semen and prostatic tissues in AIDS patients who died ***(36)***. In this study, levels of inflammation were determined by the expression of CD68 and CD20, and cellular proliferation was determined by expression of Ki67. The authors demonstrated that HHV-8 is present in normal prostates of men with HIV and that the expression of viral proteins is associated with increased localized inflammation.

Other etiologic agents reported as causing prostatitis in patients with HIV include *Cryptococcus neoformans, Aspergillus fumigatus*, adenoviruses, and cytomegaloviruses, among others. The etiology of pathogens in patients with HIV is diverse. The most important consideration when treating patients with HIV for prostatitis is their current immune status, that is, whether they are immunocompromised or not (nonprogressive disease or reconstituted with HAART) ***(37)***. In the HIV-positive patient population, there is a greater likelihood for atypical pathogens, including fungi, tuberculosis, anaerobes, and viruses. The patient with HIV is at increased risk for the development of prostatic abscess and urosepsis than the general population. There is no general agreement on management of these patients; however, it appears that restoration of the immune status by HAART is of paramount importance. Prostatic abscess formation needs to be diagnosed and if present treated accordingly.

5.4.3 Brucellosis

Brucellosis is a zoonotic disease that causes systemic symptoms and can involve many organs and tissues. The major sources of infection are consumption of unpasteurized diary products and occupational contact. Brucella is a small, gram-negative coccobacillus that grows slowly in vitro. There are four species of brucella that are pathogenic for humans. Brucella melitensis is probably the most frequent encountered organism. Diagnostic testing includes culture isolation from blood, tissue specimens, body fluids, and bone marrow; serology; and polymerase chain reaction, which has been shown to be sensitive for the diagnosis of acute disease ***(38)***. The clinical presentation is heterogenous, comprising involvement of the musculoskeletal system and organ related symptoms. Prostatitis caused by Brucella spp., however, is rarely reported in the literature. The standard treatment for acute and chronic brucellosis is a combination of doxycycline with a second drug such as rifampicin or gentamicin, in order to cure, prevent complications and relapse.

Andriopoulos et al. reported a case series of 144 patients with brucellosis ***(39)***; 13% had genitourinary involvement. The authors conclude that brucellosis is an infection with multiple presentations and, whether in an endemic region or not, a thorough history of exposure and clinical suspicion are required because thresholds in serological evaluation may lead to misdiagnosis and withholding of adequate treatment.

6 Conclusion

Acute bacterial prostatitis is a rare, well-described entity in which management is rather straightforward. Complications are nowadays rare and can be managed with minimal invasiveness in most cases. Special etiology and patient groups, such as HIV-infected patients, however, pose difficulties in diagnosis and treatment. Further research in clinical and basic aspects of this disease should be conducted to improve our understanding.

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Chapter 3
Chronic Bacterial Prostatitis

Wolfgang Weidner, Florian M. E. Wagenlehner, and Kurt G. Naber

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Summary In only about 10% of men with symptoms of chronic prostatitis/chronic pelvic pain syndrome can bacterial infection of the prostate be demonstrated by the Meares & Stamey 4-glass or the pre and post prostate massage (PPM) 2-glass test. Chronic bacterial prostatitis is mainly caused by Gram-negative uropathogens. The role of Gram-positives, such as staphylococci and enterococci, and atypicals, such as chlamydia, ureaplasmas, mycoplasmas, are still debatable. For treatment, fluoroquinolones are considered the drugs of choice because of their favorable pharmacokinetic properties and their antimicrobial spectrum. Because relapse and reinfection are major problems in chronic bacterial prostatitis, only the results of studies with a follow-up period of at least 6 months are meaningful. Analyzing the concentrations of various fluoroquinolones in prostatic and seminal fluid as well as in prostatic tissue, however, it becomes obvious that the fluoroquinolones differ not only in plasma concentrations but also in their penetration ability to these sites. Nevertheless, overall the concentrations at the site of infection of most of the fluoroquinolones with this indication should be sufficient for the treatment of chronic bacterial prostatitis and vesiculitis caused by highly susceptible pathogens. However, the increasing resistance of *Escherichia coli*, the most frequent uropathogens, against fluoroquinolones in many countries is of great concern.

Keywords Chronic bacterial prostatitis; urinary tract infection; antibiotics.

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1 Introduction

The prostatitis syndrome is one of the most common entities encountered in urologic practice. Classification of the prostatitis syndrome is based on the clinical presentation of the patient, the presence or absence of white blood cells in the expressed prostatic secretion (EPS), and the presence or absence of bacteria in the EPS ***(1)***. Prostatitis is described as chronic where symptoms are present for at least 3 months. The classification of the prostatitis syndrome is best performed by the National Institute of Diabetes and Digestive and Kidney Diseases/National Institutes of Health (NIH) ***(2)***. Category II chronic bacterial prostatitis is caused by chronic bacterial infection of the prostate with or without prostatitis symptoms and usually with recurrent urinary tract infection (UTIs) caused by the same bacterial strain. Chronic bacterial prostatitis is the most frequent cause for recurrent UTI in young- and middle-aged men.

2 Epidemiology

The incidence of bacterial prostatitis in a managed care population may be greater than previously reported ***(3)***. A recent study evaluated new physician-diagnosed prostatitis cases in a managed care population during a 2-yr interval ***(4)***. The incidence of acute or chronic bacterial prostatitis in this study was 1.26 cases per 1000 men per year.

3 Pathogenesis

The bacteriology of chronic bacterial prostatitis has been described in carefully investigated patients from tertiary care institutions ***(5,6)***. Similar to the experience with acute prostatitis, these series report that facultative Gram-negative bacilli (especially *Escherichia coli*) were responsible for the great majority of cases. Recently, reports from clinical series of patients used to support approval of antibiotics for treatment of chronic bacterial prostatitis have reported a preponderance of Gram-positive cocci ***(7,8)***. In these latter series, the median duration of patients' symptoms was 3.5 wk. One recent report describes that cultures suggesting localization of Gram-positive bacteria are not consistent in more than 90% of patients ***(9)***. Thus, the distribution of bacteria causing chronic bacterial prostatitis is currently the subject of active debate (Table 1). Unusual bacterial infections of the prostate, e.g. with Mycobacterium tuberculosis, Brucella melitensis, or fungal and viral infections especially in immuncompromised patients, for example, AIDS, are discussed in the chapter on acute bacterial prostatitis.

Table 1 The most common pathogens in prostatitis (5)

Etiologically recognized pathogens	Organisms of debatable significance
Escherichia coli	*Staphylococci*
Klebsiella spp.	*Chlamydia trachomatis*
Proteus mirabilis	*Ureaplasma urealyticum*
Other pathogens of the *Enterobacteriaceae* family	*Mycoplasma hominis*
Enterococcus faecalis	
Pseudomonas aeruginosa	

4 Evaluation

4.1 Investigation of Urine Cultures and EPS

For the proper diagnosis of chronic bacterial prostatitis (NIH category II) quantitative segmental bacteriological localization cultures and microscopy of EPS, as described by Meares and Stamey, is essential ***(10)***. Using standing techniques including the 4-glass test, the Giessen cohort study demonstrated the evidence of proven chronic bacterial prostatitis in 4.2% of 168 men ***(11)***. This figure is lower than the 7% of 656 patients in the first study 10 years before ***(5)***. *E. coli* was the predominant strain.

Nickel et al. ***(12)*** conducted a study to evaluate a simpler screening test to assess inflammation/infection, the 2-glass pre- and post-massage test (PPMT), and compare it with the 4-glass test for the initial evaluation of men with a clinical diagnosis of chronic prostatitis/chronic pelvic pain syndrome ***(12)***. A total of 353 men enrolled in the NIH Chronic Prostatitis Cohort study with complete values for baseline leukocytes counts and 2-day bacterial cultures on the 4-glass specimens were evaluated. A receiver operating characteristics curve was constructed to determine the optimal cut point of white blood cells in VB_3 predicting white blood cells in EPS. The PPMT has a strong concordance with the 4-glass test and is a reasonable alternative when EPS cannot be obtained or when microbiological assistance is not available, because EPS, as a result of its usually small volume, has to be processed and plated immediately on the spot.

A comprehensive survey describes the study results in 40 men with chronic bacterial prostatitis (NIH category II) due to, *E. coli* infection and fluoroquinolone therapy ***(13)***. In these patients, semen cultures were also achieved and demonstrated significant bacteriospermia ($>10^3$/mL) in 21 of 40 men before treatment. Thus, semen cultures identify significant bacteriospermia in only about 50% of semen specimens from men with chronic bacterial prostatitis. Therefore, semen culture of the ejaculate alone is not sufficient to diagnose chronic bacterial prostatitis ***(13)***.

4.2 Additional Investigations

In the additional workup complicating factors for UTI and bacterial prostatitis should be evaluated. Basic investigation would be uroflowmetry and residual urine. If a urodynamic disturbance is suspected further urodynamic workup should be conducted.

5 Treatment

5.1 Antimicrobial Treatment

For effective antimicrobial therapy, the pathogens at the site of infection must be exposed to a drug concentration that is sufficiently high enough to inhibit bacterial growth or even eradicate the pathogens from that site. The fluoroquinolones are considered the drugs of choice for the antimicrobial treatment of chronic bacterial prostatitis and vesiculitis.

5.1.1 Theoretical Considerations

The drug penetration is supposedly a passive transport mechanism consisting of diffusion and concentration ***(14,15)***. Drug characteristics that determine simple diffusion are concentration, lipid solubility, degree of ionization (biological membranes do not allow the passage of charged substances), degree of protein binding, and the size and shape of the molecule (small water-soluble molecules can cross biological membranes as part of the free water diffusion).The presence of a pH gradient across a biological membrane introduces the phenomenon of ion trapping. In a stable system, the uncharged fraction of a lipid-soluble drug equilibrates on the two sides of the membrane, but the charged fraction is greater on one side or the other, depending on the pH. The greatest drug concentration (sum of charged and uncharged fractions) is on the side with the higher degree of ionization. Thus, a weak base, like trimethoprim with a pKa of 7.4, will be concentrated in an acid prostatic fluid ***(16)***, but not in an alkaline mileu, like seminal fluid. The pH of prostatic fluid in patients with chronic bacterial prostatitis is, however, also often alkaline, thus concentrations of trimethoprim in prostatic secretion may be inadequate ***(15,16)***.

The fluoroquinolones in clinical use are neither pure acids nor bases but have characteristics of both amphoteric or zwitter-ionic drugs ***(17,18)***. Most quinolones that are amphoteric drugs have two ionizing groups, one positively and one negatively charged, and thus two pK_a values (Table 2) ***(18)***. At one pH value, which is between the two pK_a values and is different for each amphoteric drug, the amount of charged drug is minimal (isoelectric point). At higher and lower pH values, more drug is charged. Because the highest drug concentration occurs on the side with a greater

Table 2 Dissociation constants of fluoroquinolones (18)

Quinolone	Pk_{a1}	Pk_{a2}
Ciprofloxacin	6.1	8.7
Enoxacin	6.3	8.7
Fleroxacin	5.5	8.1
Gatifloxacin	6.0	9.2
Levofloxacin	6.1	8.2
Lomefloxacin	5.8	9.3
Moxifloxacin	6.4	9.5
Norfloxacin	6.3	8.4
Ofloxacin	6.0	8.2
Pefloxacin	6.3	7.6
Sparfloxacin	6.3	8.8

Table 3 Median concentrations in prostatic fluid and fluid to plasma ratios (F/P) of fluoroquinolones (normalised to a dose of 400 mg). Ordered according to F/P ratios

Quinolone	Dose (400 mg)	Time (h)	Subjects (n)	Fluid (mg/L)	Ratio F/P	Reference
Norfloxacin	PO	1–4	7	0.08	0.10	***(42)***
Ciprofloxacin	IV	4	8	0.18	0.20	***(42)***
Fleroxacin	PO	2–4	8	1.00	0.28	***(42)***
Levofloxacin	PO	3	8	1.42	0.29	***(43)***
Ofloxacin	IV	4	5	0.66	0.33	***(42)***
Enoxacin	PO	2–4	10	0.29	0.39	***(42)***
Lomefloxacin	PO	4	7	1.38	0.48	***(42)***
Gatifloxacin	PO	4	7	1.03	1.29	***(21,44)***
Moxifloxacin	PO	3–4	8	3.99	1.57	***(45)***

PO – per oral; IV – intravenuous

degree of ionization, drugs with an isoelectric point close to plasma pH should concentrate in fluids with a pH above and below plasma pH. The prostatic fluid to plasma concentration ratios of various fluoroquinolones were measured in healthy volunteers. Most of the fluoroquinolones show ratios below unity ranging from 0.10 to 1.57 (Table 3) ***(19–21)***. However, the concentration of most of the fluoroquinolones in the alkaline seminal fluid exceeds that in plasma (Table 4). Other studies have examined fluoroquinolone concentrations in prostatic tissue obtained at transurethral resection and they appear to be consistently at or above corresponding plasma concentrations ***(22)***. Prostatic tissue is a mixture of different compartments and might not resemble the proper localization of the infection in chronic bacterial prostatitis. Therefore, the prostatic fluid should be investigated. Macrolides also penetrate into prostatic and seminal fluids very well ***(14,23)***. Selection of an appropriate antimicrobial agent that has optimal pharmacokinetic properties for prostatic secretion and tissue is important.

Although it remains unproven in humans, considerable evidence suggests that bacteria in prostatic tissue survive in a milieu protected by biofilms. Antimicrobial agents, particularly the fluoroquinolones and the macrolides, that are more active

Table 4 Median concentrations in ejaculate/seminal fluid and fluid to plasma ratios (F/P) of fluoroquinolones (adjusted to a dose of 400 mg). Ordered according to F/P ratios

Quinolone	Dose (400 mg)	Time (h)	Subjects (n)	Fluid (mg/l)	Ratio F/P	Reference
Moxifloxacin	PO	3–4	10	2.43	1.0	submitted
Gatifloxacin	PO	4	8	1.75	1.0	***(21,44)***
Levofloxacin	PO	3	8	5.14	1.0	***(43)***
Lomefloxacin	PO	4	5	2.03	1.2	***(42)***
Fleroxacin	PO	2–4	8	5.80	1.7	***(42)***
Enoxacin	PO	2–4	11	2.19	2.2	***(42)***
Ofloxacin	IV	4	6	2.05	4.0	***(42)***
Ciprofloxacin	IV	4	8	5.06	7.1	***(42)***

PO – per oral; IV – intravenous

in biofilm than other antimicrobials, for instance, betalactams or aminoglycosides, may be preferred drugs.

5.1.2 Studies in Volunteers

The pH of prostatic fluids in healthy volunteers is usually slightly lower than plasma pH, as has been shown in various studies ***(24–27)***. In addition, the pH of prostatic secretion from men with prostatic infection is markedly increased (mean pH 8.34). It was confirmed by other studies ***(24,26)***, that the pH of prostatic fluid in patients with chronic bacterial prostatitis is rather alkaline than acidic and therefore significantly different from the secretions with lower pHs observed in healthy human males. Because the pH gradient is crucial to the ion-trapping phenomenon, one cannot apply the results obtained in experimental studies in dogs to humans, because the pH of the dog prostate might be different than human. Moreover, it is questionable whether the trapped (and charged) fraction of a drug would have any significant antibacterial effect since it may not penetrate the bacterial wall.

Because of the high drug concentration in the urine, contamination with urine is a problem in human studies. Prostatic fluid can usually be obtained by prostatic massage in small amounts only. Even a low amount of contamination with urine containing high concentrations of the drugs can therefore alter the results tremendously.

To study prostatic fluid drug levels in volunteers, a method was developed to rule out or at least to indicate possible urinary contamination ***(21)***. The subjects were not allowed to void urine after drug intake until the prostatic fluid sample was taken. In addition, a renal contrast medium, for example ioxitalamic acid or iohexol, excreted almost exclusively by glomerular filtration was administered intravenously at the same time as the drug and served as an internal standard. In most experiments, the prostatic fluid-to-plasma concentration ratios for the contrast medium were very low and markedly below unity. From these concentrations, a maximal theoretical urinary contamination can be calculated, assuming that the concentrations of these markers in prostatic fluid are negligible. However, such experiments after antimicrobial dosing can only be done up to 4 h because then the subject has to void, resulting in urinary contamination of the urethra.

According to the prostatic fluid concentrations/plasma concentration ratio, the following ranking of fluoroquinolones (from low to high) can be observed: norfloxacin, ciprofloxacin, fleroxacin, levofloxacin, ofloxacin, enoxacin, lomefloxacin, gatifloxacin, and moxifloxacin (Table 3). Correlating the prostatic fluid/ plasma concentration ratio with the isoelectric points of the fluoroquinolones, a significant positive correlation can be found (Fig. 1). This might emphasize the importance of a mechanism such as ion trapping for penetration of fluoroquinolones in the prostate.

5.1.3 Studies in Patients

5.1.3.1 Experimental Studies

Drug concentrations in prostatic tissue usually are measured in patients undergoing resection of the prostate and thus actually represent concentrations in prostatic adenoma tissue. In general the prostatic tissue concentrations exceed the corresponding plasma concentrations. These concentrations are a mixture of interstitial fluid, intracellular fluid (glandular, interstitial and smooth muscle cells), prostatic fluid, and blood. Therefore, the interpretation of such concentrations is difficult.

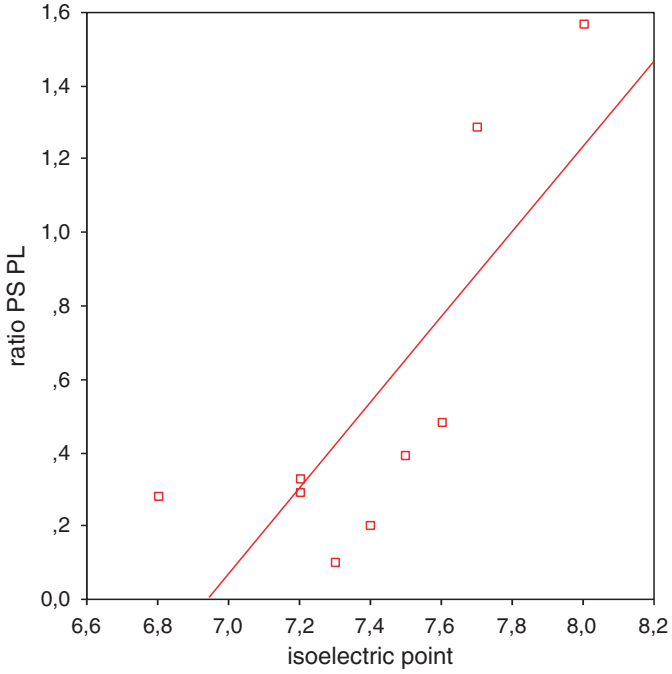

Fig. 1 Positive correlation of the isoelectric points and the prostatic secretion/ plasma ratios (PS/PL) of nine quinolones (**Table 3**) (Pearson correlation, $p = 0.013$)

5.1.3.2 Clinical Studies

Most studies in patients with chronic bacterial prostatitis have not been well controlled and have been variably designed ***(22,28)***. As a result, comparison is difficult. Duration of therapy has ranged from 14 to 150 days, and follow-up investigations have not been standardized. Because relapse and reinfection are commonly observed in these patients, only the results of studies with a follow-up of at least 6 months should be taken into consideration ***(28)***. In this respect, most experience has been gathered with ciprofloxacin (Table 5) ***(29–35)***. Overall, it appears that 60–80% of patients with, *E. coli* and other Enterobacteriaceae can be cured with a 4- to 6-week course of therapy. However, prostatitis caused by *Pseudomonas aeruginosa* and enterococci often fails to respond to treatment. Newer fluoroquinolones, like levofloxacin, gatifloxacin, or moxifloxacin, with improved activity against Gram-positive and so-called atypical pathogens, have not yet been tested in suitable clinical trials with long-enough follow-up periods. In a recent study, levofloxacin 599 mg once daily was compared with ciprofloxacin 500 mg twice daily during a 4-wk treatment. The microbiological follow up went only up to 4 wk, but the clinical follow up period comprised 6 months. In essence the study showed that with these dosages equivalent efficacy could be achieved in microbiological as well as clinical respect ***(7)***.

5.1.4 Duration of Antibiotic Treatment

In chronic bacterial prostatitis, an oral fluoroquinolone should be given for at least 4–6 wk after the initial diagnosis. After treatment, the patient should be reassessed periodically to determine appropriate treatment ***(36)***. Relatively high doses are needed, and oral therapy is preferred. Chronic bacterial prostatitis can be a relapsing illness, and recurrent episodes are best managed by either continuous low-dose suppressive therapy with an effective regimen such as fluoroquinolone intermittently whenever symptoms recur. Treatment with intraprostatic injection of antimicrobials

Table 5 Eradication of pathogens (bacteriologic cure) in patients with chronic bacterial prostatitis treated with fluoroquinolones. Only studies are listed in which the diagnosis was derived from application of the Meares and Stamey technique and a follow-up of at least 6 months was available

Quinolone	Daily dosage (mg)	Duration of therapy (days)	Number of evaluable patients	Bacteriologic cure (%)	Duration of follow-up (months)	Year of study	References
Norfloxacin	800	28	14	64	6	1990	***(33)***
Ofloxacin	400	14	21	67	12	1989	***(29)***
Ciprofloxacin	1000	14	15	60	12	1987	***(30)***
Ciprofloxacin	1000	28	16	63	21–36	1991	***(31)***
Ciprofloxacin	1000	60–150	7	86	12	1991	***(32)***
Ciprofloxacin	1000	28	34	76	6	2000	***(34)***
Ciprofloxacin	1000	28	78	72	6	2001	***(35)***
Lomefloxacin	400	28	75	63	6	2001	***(35)***

is not recommended because it is supported only by anecdotal reports. Efforts to resect infected prostatic tissue, particularly prostatic calculi, to affect a surgical cure is rarely successful and should only be carried out with very specific indications.

5.2 Additional Treatment

The combination of antimicrobials and alpha-blockers has been tested in a clinical study and improved the clinical results ***(37)***.

5.3 Management of Recurrent UTIs in Men

Acute uncomplicated UTIs in otherwise-healthy adult men between the ages of 15 and 50 years is very uncommon. Chronic bacterial prostatitis is the most frequent cause for recurrent urinary tract infections in young and middle aged men. Typically, the infections recur with the same organism. Scientific data on treatment of this entity are scarce. A fluoroquinolone with good urinary excretion and prostatic penetration should be elected for therapy, and such men should receive, at a minimum, a 7-day antibiotic regimen for the acute episode.

5.3.1 Antimicrobial Treatment

There have been a few older studies using other antibiotics (trimethoprim/ sulfamethoxazole, norfloxacin, cephalexin, ampicillin, carbenicillin, or tetracycline) suggesting that longer treatment courses, up to 12 weeks, achieve better cure rates ***(38)***. At least if prostatic involvement is suspected, a 4-week treatment regimen should be used. UTIs and recurrent UTIs in men should be treated with high dosages of oral fluoroquinolones. A dosage regimen of 500 mg ciprofloxacin twice daily, 500 mg levofloxacin once daily, or 400 mg gatifloxacin once daily may be considered comparable. Ciprofloxacin (750 mg twice daily) and levofloxacin (750 mg once daily or 500 mg twice daily) could even be increased in cases due to less susceptible uropathogens, such as, *P. aeruginosa*.

5.3.2 Antimicrobial Prophylaxis

As with recurrent UTIs in women, a continuous low-dose antibiotic prophylaxis in male patients with recurrent UTIs may as well be a possible alternative, if the episodes of UTIs recur more than three to four times a year. In special circumstances, such as patients with spinal cord lesions or catheter associated UTI, studies have shown, that prophylaxis with low doses of ciprofloxacin (100 mg or 250 mg once daily) were effective in reducing symptomatic urinary tract infections ***(39,40)***.

The emergence of resistant bacteria was not noted to be significant in these studies. In one study of patients undergoing transurethral resection of the prostate, however, ciprofloxacin-resistant, *E. coli* were detected in the feces in 1 of 21 patients after a single oral dose of 500 mg ciprofloxacin for prophylaxis ***(39)***; however, no screening was performed for low-level resistant isolates. Because resistance to fluoroquinolones is a multistep process, in carefully designed studies, the appearance of low-level resistant isolates has to be noted.

5.4 Antibiotic Resistance of Fluoroquinolones

In 1963, nalidixic acid was introduced as the first quinolone for the treatment of UTIs. Fluorination at position 6 of the quinolone structure resulted in the fluoroquinolones and significantly enhanced antibacterial potency. The fluoroquinolones target two essential bacterial enzymes, the DNA gyrase and DNA topoisomerase. Gyrase controls DNA supercoiling and relieves topological stress arising from the translocation of transcription and replication complexes along DNA. Topoisomerase IV is a decatenating enzyme that resolves interlinked daughter chromosomes after DNA replication. Both enzymes are required for cell growth and division and, therefore, the fluoroquinolones are bactericidal ***(41)***. UTIs and prostatitis have for a long time been a major indication for fluoroquinolones. Today, we note a worldwide increase of resistant pathogens against fluoroquinolones. Despite the high activity of fluoroquinolones against uropathogens, the increasing resistance rates render these agents partially ineffective again.

5.5 Selection of the Appropriate Antimicrobial Drug

The selection of the appropriate antibacterial drug in the treatment of chronic bacterial prostatitis is critical. Because of their favorable pharmacokinetic and pharmacodynamic properties, fluoroquinolones are suitable drugs. The various fluoroquinolones, however, differ not only in plasma concentrations and urinary excretion but also in their penetration ability into body fluids, like prostatic and seminal fluid, and overall also in tissue penetration. This could not entirely be explained by the differences in their dissociation constants and their pH of the isoelectric points. Several reasons must be considered, including an active secretion mechanism. In general, the concentrations in urine are much higher and the concentrations of most fluoroquinolones in prostatic fluid are well below their corresponding plasma levels. In the case of marginal drug levels in plasma, the drug concentration in prostatic fluid might not exceed the minimal inhibitory concentration of the causative pathogen for a sufficient period of time.

In addition, it has to be considered that the antimicrobial concentrations in these body fluids or tissues cannot simply be extrapolated to the minimal inhibitory concentrations of the pathogens. For example, the existence of a prostatic factor inhibiting

the antibacterial effect of some drugs and the presence of biofilm might greatly increase the minimal inhibitory concentrations for the pathogens and thereby also contribute to poor clinical results. Thus, in spite of intensive investigation we still know little about the mechanisms that govern the transport of antibiotic drugs into and their activity in the various prostatic compartments.

The results of pharmacokinetic studies on urinary excretion, drug penetration into prostatic, and seminal fluid and prostatic tissue have shown that each fluoroquinolone agent has to be considered separately. The results can be used to design meaningful clinical studies, but they cannot substitute them, because many other parameters may also influence the clinical outcome.

6 Conclusion

A careful clinical and microbiological investigation is necessary to diagnose chronic bacterial prostatitis, which is a chronic infection of the prostate with "prostatitis"-like symptoms or/and recurrent urinary tract infection. Fluoroquinolones are the antimicrobials of choice because of their favorable pharmacokinetic properties and their bacterial spectrum. The concentrations at the site of infection of most of the fluoroquinolones with this indication should be sufficient for the treatment of chronic bacterial prostatitis and vesiculitis caused by susceptible pathogens. Nevertheless, it is still difficult to treat successfully infections with less susceptible pathogens, such as, *P. aeruginosa* or Gram-positive pathogens.

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Chapter 4
Prostatitis in the Immunocompromised Patient

Alain J. Duclos

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Summary Prostatitis in the immunocompromised patient can be challenging for the caregiver. The immunocompromised state (solid-organ transplant, steroid use) of such patients can make them susceptible to organisms for which the physician is not as familiar in terms of presentation, diagnosis, and treatment. The following chapter will review the current literature on fungal, viral, parasitic, and bacterial infections of the prostate that can be encountered among patients with an abnormal immune system. Presentation, diagnostics, and treatment will be presented and discussed.

Keywords Prostatitis; immunocompromised; HIV; fungal prostatitis; viral prostatitis.

1 Introduction

In day-to-day practice, the diagnosis and treatment of prostatitis is not easy, especially when facing its chronic manifestations. Prostatitis in an immunocompromised patient presents a number of challenges to medical caregivers. Among others, the specific etiologic agents are sometimes organisms rarely encountered and, thus, are less familiar to the physician in terms of treatment options and diagnostic tests. The presentation can also be confusing, ranging to mild symptoms and signs to life-threatening emergency.

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One must also pay attention to the underlying etiology responsible for the immunocompromised state. With little exception, in the 1990s, immunosuppression was synonymous with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS). Thanks to the development of antiretroviral drugs, profoundly immunosuppressed individuals with HIV/AIDS are much less common nowadays in parts of the world in which access to these drugs is possible. Immunosuppression nowadays is likely to be iatrogenic, as in solid-organ transplant (SOT) patients or in patients with prolonged corticosteroid treatment. Although it may be more difficult to appreciate, patients with chronic diseases (long-standing diabetes, liver failure) or malignancy are likely to harbor some degree of immune dysfunction.

Organisms that rarely cause prostatitis in immunocompetent hosts can cause significant disease in immunocompromised patients. Organisms such as yeast, fungi, and viruses will be the focus of this chapter. Presentation, diagnosis, and recommendations for treatment will be presented in details.

2 Cryptococcus

Cryptococcus neoformans is an encapsulated budding yeast with a worldwide distribution. It is commonly associated with bird excreta, notably pigeons ***(1)***. Given the central role of cell-mediated immunity in the defense against Cryptococcus ***(2,3)***, it predominantly causes infections in individuals with abnormal cell-mediated immunity ***(4)***. Infection generally disseminates hematogenously from the lower respiratory tract ***(5)***, although a primary urinary tract infection has been postulated in some cases ***(6,7)***. The organism will most commonly affect the central nervous system, although other part of the body may also be affected ***(4)***.

Cryptococcal prostatitis has been well documented in the literature and generally follows disseminated disease, through a hematogenous, descending urinary route. It is rare in immunocompetent individuals ***(6)***. Two reports have described prostatic sequestration of the organism after successful treatment of disseminated cryptococcosis in a kidney transplant recipient ***(8)*** and in a patient with HIV/AIDS ***(9)***. The organism can then be released from the prostate, causing recurrent infection, either as part of the natural evolution of the underlying disease (HIV/AIDS) or after urologic instrumentation ***(8,9)***.

Presentation of cryptococcal prostatitis does not differ from more usual prostatitis and urinary symptoms predominate, ranging from mild prostatism (frequency, urgency, difficulty initiating a stream) to urinary tract obstruction. Symptoms have generally lasted for a few months and many failed courses of antibacterial therapy may have been attempted. Generally, a predisposing underlying medical condition exists: steroid or other form of immunosuppresive therapy ***(10)***, HIV/AIDS ***(11)***, leukemia ***(12)***, chronic disease (diabetes mellitus, liver disease) ***(13)***, or SOT ***(14)***. On physical examination, a low-grade temperature may be present in the patient, and the prostate is frequently enlarged, firm, nodular but generally nontender. Prostate-specific antigen (PSA) is frequently elevated, indicating inflammation of the prostate gland with disruption of the prostatic acini structure, leaking PSA in the circulation. PSA generally returns to baseline after successful treatment ***(14)***.

Definitive diagnostic requires proof of the organisms, usually demonstration of the organism in tissue section. Specific urine and blood culture may be negative. Cryptococcal antigen (cryptola LA antigen) may be elevated in blood. Keeping in view the central nervous system tropism of the microorganism, examination of the cerebrospinal fluid should be carried out, even in the absence of neurological symptoms. Transrectal ultrasound (TRUS) of the prostate may help identify an abscess of the prostate ***(15)***.

Treatment of cryptococcal prostatitis is the realm of case reports but is generally effective. Although fluconazole at doses ranging from 200 to 600 mg daily achieves serum and prostatic secretion level above minimal inhibitory concentration of most clinical isolates, amphotericin B deoxycholate and/or flucytosine is generally recommended for patients in whom an obvious cause of immnosuppression is identifiable (HIV/AIDS, SOT) ***(16)***. The exact duration of treatment is not known, ranging from 1 to 6 months in published literature. Maintenance therapy with fluconazole is recommended, although specific proof of its usefulness in this context remains to be determined. Treatment failures with fluconazole alone have nonetheless been reported, and vigilance is recommended ***(17)***. Abscesses may require surgical drainage or transurethral resection ***(18)***.

3 Aspergillus

More than 900 species of Aspergillus are reported, with less than 20 causing diseases in humans. The three most commonly implicated in human disease *are Aspergillus fumigatus, Aspergillus flavus*, and *Aspergillus niger*. Aspergillus has a worldwide distribution and can be found in soil, associated with decomposing vegetation.

A. fumigatus is usually an airborne pathogen that will primarily infect the lungs. Systemic fungemia may result from a hematogenous spread initiating in the lungs. Primary genitourinary (pyelonephritis or cystitis) aspergillosis is most frequently observed in the context of patients with a long indwelling urinary catheter. Risk factors include chronic disease (diabetes mellitus or advanced malignancy), long-term antibiotic use, immunosuppression (HIV/AIDS, SOT, long-term steroid use) or indwelling bladder catheter.

Prostatic aspergilla is a rare occurrence, with only a handful of cases described, the majority in immunocompromised patients ***(19–22)***. Patients may present with symptoms of mild prostatism to urinary retention and temperature may accompany the clinical picture. Urinalysis usually reveals elevated white blood cells or the presence of yeasts; however, routine urine culture for fungi is generally negative. Digital rectal examination (DRE) of the prostate may reveal a nodular, enlarged prostate that can be tender. Blood cultures are generally negative and PSA is increased, pending that a previous value is available for comparison. Definitive diagnosis is generally made with demonstration of fungal hyphae in tissue samples.

Treatment aspergillosis prostatitis is again the realm of case reports. Transurethral resection of the prostate (TURP) was also frequently performed in the few cases reported and may be enough to cure isolated prostatic aspergillosis ***(20)***. However, disease affecting many organs requires systemic antifungal therapy. Invasive aspergillosis

is highly lethal in the immunocompromised patients, even with adequate therapy: work-up must be prompt and treatment aggressive. It may be wise to initiate therapy in severely sick patients without definitive proofs, based on clinical judgment. Intravenous treatment with amphotericin B deoxycholate is recommended in rapidly progressive disease. Itraconazole is probably not a treatment of choice for invasive aspergillosis, with up to 40% of patients not responding to treatment ***(23,24)***. Fluconazole (200 mg BID), amphotericin B deoxycholate (total dose 240 mg) or amphotericin B lipid complex (total dose 5 g) have all been used with success in those patients. Caspofungin, a new class of antifungal agent has been used with success to treat systemic aspergillosis, but its use has never been reported in prostatitis.

Duration of treatment has not been standardized ***(25)***. However, treatment is generally continued for 6–12 months after resolution of symptoms. Patients with recurrent infections may require life-long prophylaxis.

4 Viral Prostatitis

Cytolomegalovirus (CMV) is a ubiquitous human herpesvirus with very high seroprevalence. Given the known sexual transmission of CMV and the high viral load found in semen ***(26)***, it may be surprising to find only three case reports of CMV prostatitis, two in patients with AIDS ***(27,28)*** and one in a patient with multiple myeloma undergoing chemotherapy ***(29)***. Presentation was nonspecific, with mild lower urinary tract symptoms (LUTS) and normal DRE. During TRUS, hypoechoic lesions may be identified and, if biopsied, will reveal dense lymphoplasmacytic inflammatory infiltrate with typical inclusion body immunoreactive with CMV-specific antibodies. Disseminated CMV in AIDS patients was associated with high mortality before the advent of potent specific antiviral agents. Initial treatment of CMV infection nowadays is based on ganciclovir and its oral analog, valganciclovir, with dosage adjusted for renal function. The ability to measure viral plasma load (CMV DNA with polymerase chain reaction) is an invaluable tool to follow the response to treatment. Among SOT patient recipients, treatment is frequently continued 2 wk after the last positive CMV DNA. Use of prophylaxis (renal function adjusted with valganciclovir or acyclovir) may be required for long period of time, especially in patients who present recurrent episodes. In a patient that is not improving with the aforementioned treatment, resistance to ganciclovir should be entertained. In vitro tests for such resistance to ganciclovir can be performed if warranted.

There is one report of herpes simplex virus (HSV) isolated from prostatic secretion. The patient was not immunocompromised and was suffering from prostatodynia ***(30)***. Taking into account the high seroprevalence of HSV, the clinical signification of HSV isolation from prostate secretion is unknown.

Adenoviruses also can cause debilitating opportunistic infections in severely immunocompromised individuals ***(31)***. There is a report of an AIDS patient dying of disseminated adenoviral infection without any urological symptoms ***(32)***. The prostatic lesions were of the necrotizing type. There is no specific treatment for

adenovirus infections. When possible, a judicious decrease in immunosuppression is the initial approach to therapy.

5 Blastomyces

Although more frequent in the nonimmunocompromised population through pulmonary manifestations, the dimorphic fungi Blastomyces dermatitidis has a more virulent course in immunocompromised populations with mortality rates as high as 30% ***(33,34)***. Up to 30% of patients affected with systemic blastomycosis can have genitourinary manifestations, most frequently involving the epididymis and the prostate ***(35,36)***. Primary prostatic blastomycosis is not as frequent ***(37)***. Symptoms may include hematospermia, LUTS, and perineal pain. Elevated antibody titers against Blastomyces antigen may be found in circulation and definitive diagnosis is made by culture or histologic identification, generally from TRUS-guided biopsy of the prostate. Severely ill patients should be treated with amphothericin B (total dose of 1–2 g) ***(38)***. Ketoconazole (400–800 mg daily) is also effective ***(38)***. Itraconazole (200–400 mg daily) is as effective as ketoconazole, with fewer side effects ***(39)***. Fluconazole does not appear effective ***(40)***. Total duration of treatment has been reported between 6 to 12 months.

6 Histoplasma

Histoplasma capsulatum is another fungi that can also infect the prostate, frequently in immunocompromised patients ***(41–43)***. Prostatic manifestations frequently follow disseminated histoplasmosis. Patients are frequently symptomatic, and the clinical picture is typically that of acute prostatitis. Imaging will frequently reveal prostatic abscess. Definitive diagnosis is through visualization of organism morphologically consistent with *H. capsulatum*. Treatment frequently has a surgical component (i.e., TURP), especially if an abscess is present. Systemic treatment is likely to be required, with amphotericin B deoxycholate recommended if patients are sufficiently ill to be hospitalized. Patients are then transitioned to itraconazole (200–400 mg daily) for 6–18 months. Fluconazole (400–800 mg daily) should only be used if patients are intolerant to itraconazole, as *H. capsulatum* can develop resistance to fluconazole during treatment. Detailed recommendations for treatment of disseminated histoplasmosis have been reviewed elsewhere ***(44)***.

7 Coccidioidomycosis

Coccidioidomycosis is an infection caused by the dimorphic fungus *Coccidioides immitis*. The disease is endemic only in certain regions of the Western hemisphere. In the United States, it includes southern Arizona, central California, southern

New Mexico, and west Texas. The endemic region also extends southward into Central and South America ***(45)***.

Coccidioidomycosis is caused by inhalation of Coccidioides spores (arthroconida). Once in the lungs, the spores transform into characteristic "spherules" and typically cause an acute respiratory infection that resolves rapidly. Immunocompromised patients are at much higher risk of disseminated coccidioidomycosis.

Coccidioidomycosis of the prostate is rare in immunocompromised individuals and is thought to follow hematogenous dissemination ***(46)***. In a recent publication, four of nine cases of coccidioidomycosis of the prostate were found in immunocompromised individuals ***(47,48)***. Most patients have a history of pulmonary coccidioidomycosis and the presentation is rather non specific, consisting of LUTS. DRE was frequently abnormal, with enlargement, tenderness or nodules. Definitive diagnosis was incidental after TURP or TRUS-guided biopsy, where typical spherules were observed. In the recent guidelines published by the Infectious Disease Society of America ***(45)***, recommended initial therapy is with oral azole antifungal agents: fluconazole (400–2000 mg daily), ketoconazole (400 mg daily) or itraconazole (400–800 mg daily). Amphotericin B deoxycholate (1–2 g total dose) is recommended for more severely ill patients.

Duration of treatment is not specified in the aforementioned guidelines. However, patients were generally treated for a minimum of 4 months, up to 1–2 years. After successful treatment, life-long prophylaxis (fluconazole) is recommended if patients experienced a recurrence. Among SOT recipients, prophylaxis based on fluconazole (400 mg daily) has been used for high-risk patients (positive serological test prior to receipt of treatment or history of coccidioidomycosis) living en endemic areas with some success ***(45)***.

8 Candidiasis

Candida species are the most common cause of fungal infections and candidemia may be associated with a high mortality rate, particularly in immunocompromised patients. Although *Candida albicans* is the most common pathogen, non-albican species, notably *Candida tropicalis, Candida glabrata*, and *Candida krusei* are becoming more common, probably secondary to a larger pool of relatively immunocompromised patients.

Primary candidiasis of the prostate is not a common finding. When found, it is generally secondary to urological manipulations or found in patients with some form of in-dwelling urinary catheter. Immunosuppression or chronic disease (diabetes) is frequently associated ***(49–56)***.

Presentation is nonspecific. Patients will frequently complain of LUTS, and fever will generally be present, albeit high-grade temperature (>40 °C) is not usual. DRE will usually report a large, soft, nontender prostate. Pyuria is the rule, and urine culture will very frequently grow Candida species. Candidemia is not frequently

present, but its presence warrants aggressive treatment. Imaging of the prostate may reveal abscess which, if present, uniformly requires surgical drainage (i.e., TURP).

Treatment of candida-associated diseases is reviewed in-depth elsewhere ***(57)***. Initial treatment is often based on amphotericin B deoxycholate (0.6-1.0 mg/kg/day intravenously [IV]), fluconazole (400 mg/day, IV or by mouth [PO]) or caspofungin (50–70 mg/day IV). Initial IV treatment is transitioned to PO fluconazole after initial signs and symptoms have subsided. Recommended duration of treatment is 14 days after the last positive culture. Again, the presence of abscess during imaging warrants surgical intervention.

9 Parasitic Infections of the Prostate

Microsporidia is used as a general term to describe obligate intracellular protozoan parasites that belongs to the phylum Microsporidia. There are more than 1200 species described, among which 14 have been identified as human pathogens. There is one case report of prostatitis caused by *Encephalitozoon hellem* in a patient with AIDs ***(58)***. The patient presented with chronic prostatitis that failed to respond to antimicrobial treatment and eventually died of disseminated encephalitozoonosis. A prostatic abscess caused, *E. hellem* by was incidentally identified during autopsy. Diagnosis of parasitic infection of the prostate requires tissue sample (TRUS-guided biopsy). However, only specialized laboratories can perform the required diagnostic tests. Treatment for disseminated encephalitozoonosis centers on albendazole (400 mg PO bid) and fumagillin (60 mg PO daily). Treatment is advocated for 14 days.

Another parasite that may be implicated in prostatitis is *Trichomonas vaginalis*. *T. vaginalis* is a common sexually transmited disease that mainly affects women. In men, it is associated with nongonoccococal urethritis, epididymitis, and infertility. Affected males are asymptomatic carriers in as much as 50% of cases. A number of studies have attempted to link the presence of *T. vaginalis* in prostatic secretions and chronic prostatitis or chronic pelvic pain syndrome ***(59–62)***. However, none of those studies were controlled and they were also subject to the usual bias of urethral contamination.

10 Bacterial Prostatitis

Despite their immunocompromised status, the organisms described so far will rarely cause infection, even in immunocompromised hosts. Most commonly, bacteria will be the main cause of prostatitis in immunocompromised patients. However, the presentation may be more striking, with more prostatic abscesses ***(63)*** and systemic complications.

In a follow-up study of 209 HIV-infected patients over the course of 2 years, bacterial prostatitis was diagnosed in 17 patients, or 8% ***(64)***. Presentation was uniformly similar, with fever, LUTS, and painful DRE. This finding represents an

80-fold increase when comparing it with a similar cohort of HIV-negative men of similar age. Among those 17 patients, prostatic abscesses were detected in 12 patients (1 at autopsy). Isolated organisms were some of the pathogens familiar to physicians, and were mostly Gram-negative: *Escherichia coli* (seven patients), *Kliebsiella pneumoniae* (two patients), *Enterobacter aerogenes* (two patients), *Serratia marcescens* (one patient), *Pseudomonas aeruginosa* (one patient), and *Staphylococcus epidermidis* (one patient). Cultures were not available for three patients. Blood cultures were positive in only two patients, with the same organism as in the urine. The high frequency of prostatic infection in these patients is surprising given the mean age of 39 in the group.

The authors hypothesized that HIV infection in itself was a risk factor, by decreasing the prostatic defenses against infection normally found in prostatic secretions. Interestingly, there was a correlation between the stages of HIV infection and the prevalence of prostatitis. In the same report, it was found that 2 of 71 cases of prostatitis were found in asymptomatic seropositive patients, 4 of 60 among patients presenting with AIDS-related complex and in 11 of 78 patients with AIDS. Patients were treated for 6–18 weeks, most frequently with a fluoroquinolone. Follow-up longer than 2 months was only available for seven patients, and five of those experienced relapses or recurrent infections, again, significantly greater than what is expected for HIV-negative men ***(65)***.

In another publication relating urological complications in AIDS patients, 6 prostatitis were described ***(66)***. The three patients with Gram-negative etiology presented with LUTS and fever and responded well to fluoroquinolones. The other three patients harbored *Staphylococcus aureus* or *Staphylococcus epidermidis* and failed initial empirical antibiotherapy. Investigation revealed abscesses in two of these patients and all patients did well after adequate antimicrobial therapy and drainage.

Among unusual bacteria, a case report exists of acute prostatitis caused by *Hemophilus parainfluenzae* ***(67)***. *H. parainfluenzae* is a frequent colonizer of the upper respiratory tract but rarely causes pathology in the urinary tract. The 29-year-old patient was HIV positive and presented with fever and LUTS. Rectal examination revealed an enlarged, boggy, and tender prostate. Urine culture grew *H. parainfluenzae*, and the patient was treated for 3 months with doxycycline, after which urine culture after prostatic massage was negative.

The Mycobacteriaceae can also cause prostatitis. With the advent of attenuated *Mycobacterium bovis* for the intravesical treatment of bladder cancer, granulomatous prostatitis is familiar to urologists. It may be present in as many as 75% of prostates after treatment with intravesical bacillus Calmette-Guérin (i.e., BCG) ***(68)*** but is, fortunately, rarely symptomatic. Among patients with AIDS, prostatic abscesses caused by *Mycobacterium tuberculosis* and *M. avium* have been demonstrated ***(69–71)***. In the reviewed cases, presentation was relatively uniform with fever and LUTS, and only one patient grew Mycobacterium in the urine. Rectal examination revealed a hard, lumpy prostate reminiscent of neoplasia. TRUS revealed abscesses in all cases, and TURP was performed. Surgical specimens were typical of caseating necrosis and grew Mycobacterium. Urinary concentration of isoniazid, rifampin, pyrazinamide, and streptomycin are high and treatment with three drugs is recommended for 6 months ***(72)***.

11 Approach to the Patient and Treatment Algorithm

The immunocompromised patient is rarely a medically simple patient, and careful examination and assessment is required. Standard laboratory together with urine and blood cultures (bacterial and fungal) should be obtained before initiation of antimicrobial treatment. The presentation of acute prostatitis (category I) is rarely subtle and a diagnosis should easily be attained. Empirical antibacterial therapy should be initiated and then tailored to culture results. In cases in which unusual organisms are isolated, it may be appropriate to consult an infectious disease specialist. Patients with acute prostatitis not responding adequately to empirical antibacterial therapy need prompt reassessment. Ensure that appropriate fungal cultures have been obtained. A TRUS is invaluable to identify prostatic abscesses and may also provide tissue for identification of fungus. Refer to the text for specific antimicrobial agent and duration of treatment for each specific etiology. The approach is summarized in Figure 1.

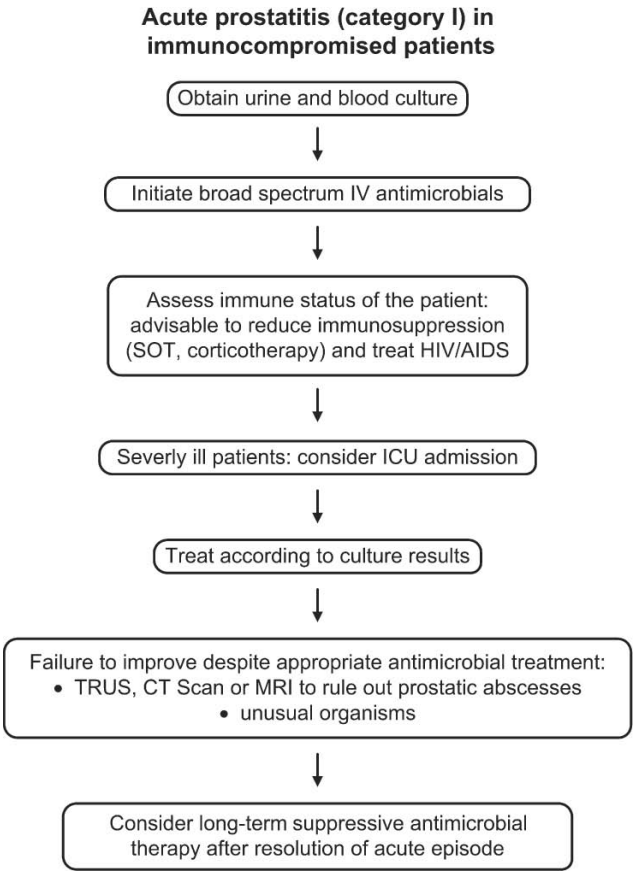

Fig. 1 Proposed approach for the diagnostic and treatment of category I prostatitis in immunocompromised patients. ICU: intensive-care unit. MRI/ magnetic resonance imaging; CT scan/ computed tomography scan

For chronic bacterial prostatitis (category II), an initial course of antimicrobial therapy is appropriate, especially in treatment naïve individuals. It should not be continued when cultures are negative or if there is no improvement in patient's symptoms. Consider early TRUS. With negative cultures, a combination of alpha blockers with antiinflammatory agents (e.g., nonsteroid antiinflammatory agents or phytotherapy) can be attempted for 3–4 months. If this is not successful, physical therapy or biofeedback can be attempted, together with pharmacological therapy aimed at chronic pain: amitryptiline or gabapentin. When all else has failed, consider referral to a pain management specialist. The approach is summarized in Figure 2. Treatment option for category III and IV are reviewed elsewhere in the present text.

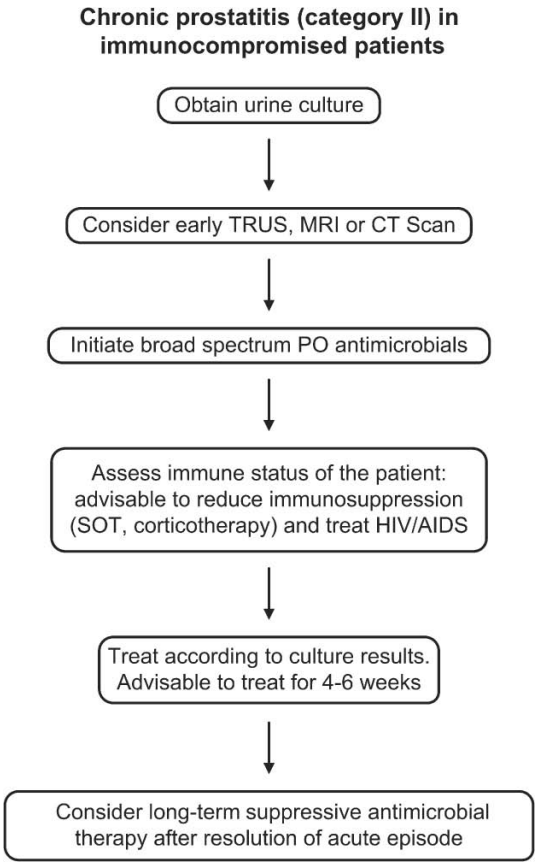

Fig. 2 Proposed approach for the diagnostic and treatment of category II prostatitis in immunocompromised patients. ICU, intensive-care unit; MRI, magnetic resonance imaging; CT scan, computed tomography scan

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Chapter 5
Quality of Life and Economic Impact of Chronic Prostatitis

Elizabeth A. Calhoun, Anna M. S. Duloy, and J. Quentin Clemens

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Summary Chronic prostatitis (CP) is a common syndrome of uncertain etiology. In the current National Institutes of Health (NIH) classification system, there are four categories of prostatitis. From 1990 to 1994, prostatitis accounted for almost 2 million outpatient visits per year, 8% of visits to urologists, and 1% of visits to primary care physicians in the United States. CP has health-related quality of life and economic implications for its sufferers and for society. For patients, the syndrome affects both physical and psychological functioning. Treatment of these symptoms may involve procedures, prescriptions, and/or frequent visits to the physician, resulting in substantial financial costs for the patient and for society. This chapter reviews the current state of knowledge about the quality of life and economic impact of prostatitis.

Keywords Prostatitis; quality of life; resource utilization; outcomes research.

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1 Introduction

Chronic prostatitis (CP) is a common syndrome of uncertain etiology. From 1990 to 1994, prostatitis accounted for almost 2 million outpatient visits per year, 8% of visits to urologists, and 1% of visits to primary care physicians in the United States ***(1)***. Chronic prostatitis remains enigmatic ***(2,3)***; its hallmark is a symptom complex of pelvic pain ***(4)*** and lower urinary tract symptoms ***(5,6)***. Among the available diagnostic tests for prostatitis, their reliability is low and none is a gold standard, and the efficacy of the most common treatments, for instance, antibiotics and alpha-blockers, is not strongly supported by existing evidence ***(7,8)***.

CP has health-related quality of life ***(9,10)*** and economic implications for its sufferers and for society. For patients, the syndrome affects both physical and psychological functioning. Specifically, symptoms of pain, urinary problems, depression, hypochondriasis, hysteria, and somaticization negatively impact the quality of life of affected individuals ***(9)***. Treatment of these symptoms may involve procedures, prescriptions, and/or frequent visits to the physician, resulting in substantial financial costs for the patient and for society. Although chronic prostatitis causes considerable distress and accounts for a significant proportion of annual outpatient physician visits, its direct and indirect costs have not been well quantified.

There are several reasons to examine the quality of life and financial burdens of, CP Burden of illness studies can help to define the distribution of resources used in treatment and help to target those patient groups most in need of health care interventions. The individual burden of disease is often measured in terms of its effect on a person's physical condition or quality of life, and the societal burden is measured in economic terms as the direct and indirect costs of illness. Direct costs primarily include the costs of medical care, whereas indirect costs include work absenteeism, decreased productivity while at work, and general economic disruption (e.g., needing help from others to complete regular tasks like childcare or yard work) ***(11)***. Measurement of relative cost data plays a particularly important role in establishing treatment priorities at a time when health care resources are increasingly scarce.

This chapter reviews the current state of knowledge about the quality of life and economic impact of prostatitis. Additionally, it examines the clinical aspects of prostatitis including the definition and prevalence, diagnosis and treatment, and quality of life impact. It also will examine the individual and social costs of prostatitis including its direct and indirect costs.

2 Clinical Aspects of Prostatitis

2.1 Definition and Prevalence

The term prostatitis can be used to describe a variety of clinical disorders, including well-defined acute and chronic bacterial infections, poorly defined chronic pelvic pain syndrome, and asymptomatic inflammation in the prostate gland. In

the current National Institutes of Health (NIH) classification system, there are four categories of prostatitis ***(12)***. Type I prostatitis (acute bacterial prostatitis) is an acute, febrile bacterial infection of the prostate that is accompanied by bacteriuria and pyuria. Type II Prostatitis (chronic bacterial prostatitis) indicates the presence of recurrent, low-grade bacterial infections of the prostate. The hallmarks of type II prostatitis include episodes of irritative voiding symptoms that are associated with bacteriuria and pyuria after prostate massage. Taken together, type I and II prostatitis account for 5–10% of all cases. Type III prostatitis (chronic prostatitis/chronic pelvic pain syndrome or CP/CPPS) refers to the presence of bothersome pelvic pain symptoms without identifiable etiology. CP/CPPS accounts for more than 90% of all cases. Common symptoms include discomfort in the perineum, suprapubic region, and penis; pain associated with sexual activity; and bladder symptoms such as urinary frequency. Type IV prostatitis (asymptomatic inflammatory prostatitis) indicates the presence of prostate inflammation in the absence of symptoms.

Several estimates of prostatitis prevalence exist because of variances in the definitions used. For example, the estimated prevalence of medically diagnosed prostatitis is 9% ***(13)***, the overall lifetime prevalence of prostatitis is 14% ***(14)***, the prevalence of a self-reported history of prostatitis is 4–16% ***(13,15,16)***, and the prevalence of chronic prostatitis-like symptoms is 10–12% ***(17,18)***. In a large nationwide sample of men, patients with prostatitis were found to be older, white, living alone, unemployed, and more likely to have a history of benign prostatic hyperplasia (BPH), a sexually transmitted disease, a vasectomy, prostate cancer in the family, severe stress at home and work, and current severe lower urinary tract symptoms ***(15)***.

2.2 Diagnosis and Treatment

Unlike for types, I, II, and IV, a gold-standard diagnostic test for type III chronic prostatitis/chronic pelvic pain syndrome does not exist. Because its etiology and pathogenesis is largely unknown, CP/CPPS is diagnosed by exclusion. The identification of a treatable cause of the symptoms is the primary goal, although for the large majority of men, no such cause will be found. Affected men therefore receive a wide range of empirical treatments, including alpha-blocker therapy, antibiotics, analgesics and physical therapy ***(19)***.The efficacy of these treatments varies ***(20–26)***, and further evaluation is needed to gain more insight into their possible benefits. The lack of a diagnostic test and of treatments that better alleviate pain and manage CP/CPPS symptoms are a source of great frustration for physicians and patients alike.

Prostatitis types, I, II, and IV, are considerably easier to diagnose. Type I is primarily diagnosed through clinical findings and a positive urine culture. Its treatment involves antibiotic therapy and if necessary, hospitalization to provide intravenous hydration and analgesics. Type II is diagnosed via the 2-glass test, which involves examination of urine from before and after prostatic massage. Its treatment, like

that of type, I., involves antibiotics. Patients with frequent recurrences can be using antibiotics for 3 to 6 months and often need treatment of bladder outlet obstruction as well. Type IV is often diagnosed by the presence of leukocytes in prostatic secretions that are collected for infertility evaluations or via prostate biopsy. Usually no treatment is recommended.

2.3 Health-Related Quality of Life

Evaluating health outcomes is important in medicine. Health outcomes include clinical outcomes, patient-focused outcomes (quality of life, functional status, satisfaction), and resource use ***(27)***. Measuring health-related quality of life (HRQOL) is particularly useful for understanding how a patient perceives his/her disease. This understanding can be used to help physicians make better clinical decisions and achieve outcomes that are more important to patients. Generally speaking, measures of HRQOL depict how well individuals function in life and their discernment of well-being ***(28)***. They are important for understanding the effects of chronic disease, determining the efficacy of treatments, and for informing policy decisions and patient management. HRQOL is both subjective and multidimensional ***(29),*** as reflected in the following contemporary definition: "Health-related quality of life refers to the extent to which one's usual or expected physical, emotional, and social well-being are affected by a medical condition or its treatment" ***(30)***.

Measurement of HRQOL is commonly achieved via questionnaire. Many different HRQOL questionnaires have been developed, and no single instrument is applicable to every setting. To select an appropriate questionnaire, there are primarily two options. The first is to choose an established questionnaire that has demonstrated reliability and validity. The second option is to create a new instrument based upon clinical knowledge of the problem. Limitations are that the first option may have omitted important questions, whereas the second may not prove to be reliable or valid. Cella and colleagues ***(31)*** recommend selecting the most clinically relevant questionnaire and tailoring it to the specific disease, condition, or treatment under study through the addition of study-specific questions.

2.4 Quality of Life Impact

Mortality and serious complications from chronic prostatitis are uncommon. Therefore CP, like other nonlife-threatening diseases, is primarily a quality of life disease. The patient's perspective of their disease is of utmost importance and the goal of treatment is to maximize quality of life. To gain a total understanding of the patient's perspective, the symptoms of chronic prostatitis and the disease-specific and general health status of patients should be examined ***(27)***. Disease-specific measures of health status can be used to determine the

impact a specific condition has on an individual, and general health measures can enable impact comparisons to be made across several different diseases and treatment groups. Where possible, data specific to type III Prostatitis (CP/CPPS) will be highlighted.

2.5 Symptoms and Symptom Measures

Many symptom indices have been developed for use in clinical research in prostatitis. In Germany, Brahler and colleagues created an 18-item "Giessen Prostatitis Symptom Score;" Krieger et al. designed a 21-item questionnaire to assess sexual dysfunction, pain, and voiding symptoms ***(32)***; Nickel and colleagues developed a 10-item symptom frequency and symptom severity questionnaire that was used in a randomized double-blind sham controlled trial of transurethral microwave thermotherapy for CP ***(33)***; Neal and Moon created a four-item questionnaire for use in an open-label study of alpha-blockage for treatment of CP ***(34)***; and Chiang and colleagues created a 10-item symptom severity score chart to measure treatment outcomes of transurethral needle ablation for nonbacterial prostatitis ***(35)***.

The aforementioned symptom indices were not considered wholly satisfactory, in part because they were not validated. Regardless, they helped to lay the groundwork for the creation of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), which is a well-accepted outcome measure for chronic prostatitis.

The NIH-CPSI was created by the Chronic Prostatitis Collaborative Research Network (CPCRN) to serve as a reliable and valid instrument for measuring CP/CPPS symptoms and quality of life impact ***(36)***. The NIH-CPSI is easily understandable; it can be self-administered in less than 5 min; has discriminative ability between CP, BPH, and control populations; and has been accepted as the primary tool for measuring the severity and evolution of CP/CPPS symptoms over time ***(36,37)***. The index has nine items and focuses on three aspects of CP/CPPS: pain, urinary symptoms, and quality of life impact. The pain domain addresses location, severity, and frequency; the urinary domain addresses irritative and obstructive symptoms; and the measure of impact on the quality of life focuses on how symptoms affect daily activities. There is a total possible score of 43, and higher scores indicate worse outcomes in all domains. The pain domain scores range from 0 to 21, urinary symptoms from 0 to 10, and quality of life impact from 0 to 12.

Many studies have used the NIH-CPSI to better quantify and understand the impact of chronic prostatitis symptoms. The index allowed Nickel and colleagues to determine the prevalence (10%) of chronic prostatitis-like symptoms among patients of family practitioners in Canada ***(17)***. Using the NIH-CPSI, Litwin et al. determined that the most fundamental component of chronic prostatitis is pain. In a group of 151 men with CP/CPPS, more than half reported perineal or abdominal pain and large numbers had pain in the testicles (40%) or in the tip of the penis (32%). Only 8% reported pain in all four areas ***(36)***.

Tripp and colleagues ***(38)*** used the NIH-CPSI to determine that urinary scores, pain intensity scores, and depressive symptoms significantly predicted quality of life in CP/CPPS patients. On average, for every one-point increase (more impairment) in urinary scores there was a corresponding 0.118 increase (poorer quality of life) in the HRQOL score; for every one-point increase in pain intensity scores there was a corresponding 0.722 increase in the HRQOL score; and for every one-point decrease (poorer mood) in depressive symptoms there was a corresponding 0.381 increase in the HRQOL score. The data show that pain intensity and depressive symptoms significantly predict a worse HRQOL in CP/CPPS patients, with pain intensity as the most robust predictor. Contrary to the results of Wenniger et al. ***(39)***, Turner and colleagues, Ku and colleagues, and Litwin and colleagues found that urinary symptoms also contributed significantly to predicting HRQOL, although their results showed that pain was more robustly associated with worse HRQOL than were urinary symptoms ***(36,40,41)***. Specifically, Ku et al. found that men who experienced mild pain had a 3.9-fold risk of poorer HRQOL and men with severe pain had a 15.7-fold risk of reduced HRQOL.

Additional measures have been used to examine the psychological impact of chronic prostatitis. Using two validated measures, The Minnesota Multiphasic Personality Inventory and the Beck Depression Inventory, investigators found that two-thirds of their study population reported anxiety and more than half reported depression. A follow-up study of the patients revealed that stress and anxiety increased with time, while social functioning and physical well-being decreased ***(42)***. Another study found that more than 50% of CP/CPPS patients met criteria for depression ***(43)***. Causality, however, was not determined. Furthermore, in an Internet survey of 163 CP/CPPS patients, 78% reported minor or major depression and 5% reported suicidal thoughts as a result of the syndrome ***(44)***.

Other studies that have examined CP/CPPS patients in relation to control populations have found that men with CP/CPPS consistently score worse than controls on hypochondriasis, depression, hysteria, and somatization scales ***(45)*** and that CP/CPPS patients can be differentiated from control populations based on depression and a tendency to somaticize ***(46)***. Pontari and colleagues ***(47)*** examined the differences between 463 CP/CPPS patients in the Chronic Prostatitis Cohort (CPC), a longitudinal study conducted by the CPCRN, and 121 asymptomatic age-matched controls ***(47)***. They found that CP/CPPS patients reported a greater incidence of psychiatric diseases, the most significant of which was anxiety/panic disorder. The incidence of depression in the CP/CPPS group was found to be 20.5%, although depression in CP/CPPS patients has ranged from 20% to 80%, with severe symptoms up to 60% ***(46,48)***. Because the psychological profile of patients before the onset of CP/CPPS is unknown, it is unclear whether CP/CPPS symptoms lead to psychiatric disease or whether psychiatric disease leads to worse CP/CPPS symptoms ***(27)***.

Studies have also shown that sexual dysfunction is greater in men with CP/CPPS than in healthy men, and can also negatively impact quality of life. Keltikangas-Jarvinen and colleagues found that 52% of their patients had periodic or total impotence or decreased libido ***(49)*** and Berghuis et al. ***(50)*** found that CP/CPPS

decreased the frequency of sexual contacts in 85% of their study population, prevented or inhibited men from establishing new sexual relationships in 43%, and interfered with, or ended, an ongoing sexual relationship in 67%. In a population-based survey ***(48)***, 17% of men reported marital difficulties as a result of their CP/CPPS.

2.6 Disease-Specific Measures of Health

The quality of life subscore of the NIH-CPSI is a disease-specific measure of HRQOL. As noted previously, the HRQOL subscore ranges from 0 to 12, with a higher score indicating worse quality of life. Results are obtained by summing patient responses to the following three questions: *How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week? How much did you think about your symptoms, over the last week? If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?* ***(36)***.

Using the QOL subscale of the NIH-CPSI, the condition-specific HRQOL was measured among 278 men in the CPC study. The subscale scores were high, indicating severe HRQOL impairment. Additionally, increasing symptom severity resulted in worsening HRQOL. Predictors of worse chronic prostatitis symptoms were found to be lower educational level and income, while a history of rheumatic disease was associated with higher scores ***(9)***.

2.7 Generic Measures of Health

Many instruments exist for generic health measurement, including the Sickness Impact Profile (SIP) ***(51)*** and the RAND Medical Outcomes Study Short Form-12 (SF-12) ***(52)***. The SIP measures sickness-related dysfunction in 12 areas: ambulation, mobility, body care and movement, social interaction, emotional behavior, alertness behavior, communication, eating, work, sleep and rest, household management, and recreation and pastimes. The SIP has been used to examine how CP/CPPS impacts patient quality of life and daily functioning. Wenniger and colleagues determined that the impact of CP/CPPS on health status is similar to that for patients with myocardial infarction, angina, or Crohn's disease ***(39)***. These results highlight the importance of evaluating sickness-related dysfunctions in patients with CP/CPPS.

The SF-12 is a 12-item generic HRQOL instrument that assesses the following domains: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. The SF-12 has two subscales: the Physical Component Summary (PCS) score and the Mental Component Summary (MCS)

score. Each subscale is scored from 0 to 100, with higher scores indicating better quality of life. Mean PCS and MCS scores are set at 50 for the general population and scores from patients with various diseases are also available ***(53)***.

HRQOL was measured in men from the CPC study using the SF-12 ***(9)***. CPC patients' MCS scores (44 ± 9.8) were worse than the scores observed in the most severe subgroups of congestive heart failure and diabetes mellitus patients, and their PCS scores (46.4 ± 9.5) were worse than the scores for the general male population. Significant independent predictors of worse mental component scores included: increased chronic prostatitis symptom severity, a history of psychiatric disease, and younger age. Independent predictors of worse physical component scores were worse chronic prostatitis symptoms and a history of rheumatologic disease.

3 Economics: Individual and Social Costs of Prostatitis

The impact of chronic prostatitis on patients' quality of life results in substantial resource consumption. CP increases healthcare expenditures both directly and indirectly. A better understanding of these costs and the economic burden of prostatitis is an important step for identifying its impact on society. Because healthcare resources are becoming increasingly scarce, controlling health expenditures is a major policy objective. Concerns about the cost of healthcare and consequently, the cost-effectiveness ratios of treatments, have become almost as important as clinical effectiveness. As economic evidence is becoming more important in medical decision-making, it is critical to conduct rigorous cost evaluations of CP and to use this information to help determine the most appropriate allocation of resources. An increased understanding of prostatitis healthcare resource use and the direct and indirect costs of CP, including inpatient hospitalizations, hospital outpatient and physician office visits, ambulatory surgery procedures, and emergency room care, will likely result in more cost-efficient management of the disease ***(54)***.

4 Health Care Utilization for Prostatitis: Results from the Urologic Diseases in America Project

As part of the Urologic Diseases in America Project, McNaughton-Collins et al. ***(19)*** analyzed numerous public and private databases to assess the use of healthcare resources by patients with prostatitis. These data include all types of prostatitis (NIH types I-IV). Results are summarized below.

4.1 Inpatient Care

Patients are not often admitted to hospital because of prostatitis, but some exceptions exist. Patients who are septic from a bout of acute bacterial prostatitis, older men

with chronic bacterial prostatitis that need management of urosepsis, and CP/CPPS patients that need pain control are likely to be admitted ***(19)***. Additionally, patients with painful urinary symptoms who have high fever, hypotension, tachycardia, and leukocytosis are commonly admitted, whereas patients with milder symptoms are frequently treated as outpatients.

The rate of inpatient hospitalization for prostatitis declined during the 1990s. Healthcare Cost and Utilization Project (HCUP) data from 1994, 1996, 1998, and 2000 shows that hospitalization rates for prostatitis increased with patients' age ***(55)***. Medicare data from the Centers for Medicare and Medicaid Services (CMS) show that the age-adjusted inpatient rates for 1992, 1995, 1998, and 2001 are between 2 and 2.5 times greater in the Medicare population than in the HCUP population ***(56)***. Data from HCUP, CMS, and the Center for Health Care Policy and Evaluation (CHCPE) ***(57)*** all show a decline in rates of inpatient hospitalization for men with prostatitis over time.

4.2 Outpatient Care

Outpatient care for prostatitis can be for diagnosis, treatment, or follow-up and includes hospital outpatient and physician office visits, ambulatory surgery procedures, and emergency room care. A slight decrease in visits for prostatitis over time can be seen across the outpatient databases. This could either be the result of a true decrease in visits for prostatitis or it could reflect a change over time in the way physicians code for prostatitis ***(19)***.

4.2.1 Hospital Outpatient Visits

Data suggest that the rate of hospital outpatient visits increased during the 1990s. National Hospital Ambulatory Medical Care Survey (NHAMCS) data for 1994, 1996, 1998, and 2000 show that the aggregate age-adjusted hospital outpatient visit rate for prostatitis between 1994 and 2000 was 195 per 100,000 patients with prostatitis listed as any diagnosis ***(58)***. The rate of outpatient visits for men aged 55 and older was nearly 2.5 times that of men aged 18–54 (375 per 100,000 versus 135 per 100,000). Although Medicare data for 1992, 1995, 1998, and 2001 show variations by year in the age group with the highest visit rate, the data show a 25% increase in the age-adjusted hospital outpatient visit rate between 1992 and 2001 ***(59)***.

4.2.2 Physician Office Visits

The rate of physician office visits declined during the 1990s. According to National Ambulatory Medical Care Survey (NAMCS) data, there was a 25% decrease in the age-adjusted physician office visit rate between 1992 and 2000 ***(60)***. The total number of physician office visits in 1992 was 2,176,818 (a rate of

2,477 per 100,000 population) and in 2000 there were 1,795,643 visits (a rate of 1,867 per 100,000 population). When looking at the aggregate age-adjusted rate for the even years between 1992 and 2000, the visit rate increased with age. Like the NAMCS data, Medicare data for 1992, 1995, 1998, and 2001 show a decrease in the rate of age-adjusted physician office visits for prostatitis patients ages 65 and older over time (2,981 per 100,000 in 1992 versus 1,828 per 100,000 in 2001) ***(59)***., which corresponds to a 40% reduction in physician office visits between 1992 and 2001. Similarly, data from the CHCPE for the even years between 1994 and 2002 show that the unadjusted physician office visit rate for men with prostatitis who had Commercial health insurance decreased over time. There was a 34% reduction in the office visit rate from 1994 to 2002 (450 per 100,000 in 1994 versus 296 per 100,000 in 2002) and the visit rate within each year of study increased with age.

4.3 Ambulatory Surgery Procedures

Visits to ambulatory surgery centers also have been decreasing. CHCPE data show that the rate of visits to an ambulatory surgery center by patients with a primary diagnosis of prostatitis and with commercial insurance decreased by 41% between 1994 and 2002 (11 versus 6.5 per 100,000). Similarly, CMS data show a decrease over time of the age-adjusted rate of ambulatory surgery visits for prostatitis patients ages 65 and older. Data from the National Survey of Ambulatory Surgery database showed that visit rates were fairly stable between 1994 and 1996 (annualized rate of 33 per 100,000 for prostatitis listed as any diagnosis), with visit rates highest for men aged 55–74 (216 per 100,000) ***(61)***. Three procedures, ranked in order of decreasing frequency, were associated with ambulatory surgery visits: cystoscopy, prostatic biopsy, and urethral dilation.

4.4 Emergency Room Visits

According to data from the CHCPE, the rate of emergency room visits by patients with a primary diagnosis of prostatitis remained fairly stable between 1994 and 2002 (at 12 per 100,000 population). Although emergency room visits were three times more common in the Medicare population than in the CHCPE population, the age-adjusted emergency room visit rate in the Medicare population decreased by 29% between 1992 and 2001 (48 per 100,000 in 1992 versus 34 per 100,000 in 2001). The highest rates within each year were among patients in the older age groups.

4.5 Economic Impact

Cost data show that, during the 1990s, a shift took place from inpatient to outpatient care. Excluding spending on outpatient prescription drugs, total expenditures on prostatitis increased by 14% between 1994 and 1998 and subsequently decreased by 8% between 1998 and 2000. Although the expenditures for ambulatory surgery and inpatient hospitalizations decreased between 1998 and 2000, expenditures for noninpatient services such as physician office visits, hospital outpatient visits, and emergency room visits all increased ***(19)***, making a shift from inpatient to outpatient care evident. This shift can also be found between 1994 and 2000, where noninpatient services accounted for an increasing percentage (25% to 31%) of the total expenditures. Predictors of more frequent healthcare visits include worse mental health, less education, urinary symptoms, more non-pelvic pain sites, and pain between the rectum and testes ***(54)***.

In the United States, an estimated $84 million was spent on treating prostatitis in 2000, according to inpatient and outpatient claims of patients with a primary diagnosis of prostatitis. This estimate consists of $35 million for inpatient services, $24 million for ambulatory surgery, $16 million for emergency room visits, and $4 million for hospital outpatient visits ***(19)***.

Treatment costs of prostatitis have increased over time. Between 1994 and 2002, mean costs increased for emergency room visits, physician outpatient visits, and inpatient hospitalization ***(57)***. In the Medicare population, total expenditures increased 1% between 1992 and 2001 from $27.1 million to $27.5 million, respectively, and outpatient services were an increasingly larger percentage (51% to 58%) of the total expenditures. In 2002, the average annual expenditure for privately insured individuals aged 18 to 64 with a medical claim corresponding to a diagnosis of prostatitis was $5,464 ($4,038 for medical care and $1,426 for prescription drugs) and $3,704 for insured individuals without a medical claim relating to prostatitis ***(19)***. The difference in expenditure, $1,759, is likely accounted for by costs directly or indirectly related to prostatitis.

5 Direct and Indirect Costs

The direct and indirect costs of prostatitis are substantial ***(62–64)***. Direct costs refer to costs associated with office visits, inpatient hospitalizations, ambulatory surgery, emergency room visits, and prescription medications. Sources of direct costs for inpatient and outpatient visits include room and board, laboratory, pharmacy, radiographic studies, physician professional fees, and operating room costs. Indirect costs include work absenteeism, decreased productivity, and economic disruption in other roles (e.g. needing helpers to complete regular tasks). Studies that have assessed the costs of prostatitis have either utilized population-based administrative healthcare records or established clinical cohorts of CP/CPPS patients.

The direct costs of CP patients are greater than those for control populations. Clemens et al. utilized administrative data from the Kaiser Permanente Northwest health maintenance organization (HMO) in Portland, OR to compare costs incurred by 5,241 men with prostatitis to a control group of similarly aged men ***(64)***. Prostatitis was defined based on a diagnosis of "chronic prostatitis" or "prostatitis not otherwise specified" in the electronic medical record system. Prescription costs, prescription fills, outpatient costs, inpatient costs, and inpatient stays were all greater for CP patients than for control populations. The mean annual total cost for CP patients was $4,387 and the mean annual total cost for the control population was $2,689. The difference in total cost is primarily due to outpatient and pharmacy expenses.

The average annual costs for individuals with prostatitis vary according to the setting. A recent study of 167 men enrolled in the CPC, a tertiary care setting, found that 82% of them had accrued some costs during the 3-month period before their enrollment in the cohort. The average man had undergone six procedures, five physician visits, and took two and a half prescriptions for his condition during the 3-month period ***(62)***. Of the men enrolled, 80% incurred direct costs and 26% had indirect costs. Procedures/tests (mean, $761) were the largest component of directs costs followed by healthcare visits (mean, $325) and medication (mean, $282). Their average total costs (direct and indirect) for the 3-month period prior to enrollment in the study were $1,099 per person, with a projected annual total cost (direct and indirect) of $4,397 per person. This cost is substantial when compared with $4,636 ***(65)***, the average per capita health expenditure in 2000 for the United States.

Similarly, costs appear high in an analysis of 62 men with CP/CPPS who were recruited from an outpatient urology clinic ***(63)***. In this study, costs were assessed using Medicare rates as well as non-Medicare (private insurance) rates. Because many men with CP/CPPS are younger than the age of 65, the latter rates may be more indicative of the true societal costs. Mean annualized direct medical costs for CP/CPPS were $3,017 (Medicare rates) and $6,534 (non-Medicare rates), with higher costs observed in subjects with more severe symptoms. Mean annualized indirect costs for CP/CPPS were $3,248, with 16 men reporting lost wages as the result of their condition during the three months prior to the study. The direct costs are similar or greater than those reported for other chronic pain conditions such as peripheral neuropathy ($917) ***(66)***, low back pain ($2,144) ***(67)***, fibromyalgia ($2,274) ***(68)***, and rheumatoid arthritis ($2,533) ***(69)***.

Considerably lower mean costs were incurred by prostatitis patients enrolled in an HMO (at $208 in the 2-month episode of care and $202 in the subsequent year for prostatitis costs) ***(54)***. This discrepancy is likely due to the fact that both the CPC and outpatient urology clinic patients were recruited from within a tertiary care setting and therefore had more chronic and severe symptoms, resulting in higher treatment use and costs than those of patients in the primary and secondary care HMO sample.

Patient behavior, in addition to setting, may affect healthcare use and costs. Turner et al. ***(54)*** found that mean costs for 270 men with a new diagnosis of prostatitis were significantly greater than age-matched controls in both the year preceding the

diagnosis ($2134 versus $1469) and the year subsequent to the diagnosis ($2410 versus $1728). However, costs specific to prostatitis were only a small portion of the total observed costs. This suggests the discrepancy may have to do with patient behavior. Further investigation into the identification of patient characteristics related to total healthcare costs, not only prostatitis-related costs, may be useful to increase understanding of high-cost patients. The difference in total costs between prostatitis and nonprostatitis patients also suggests that seeking care for prostatitis is part of a broader pattern of healthcare use for multiple medical problems. A possible explanation is that patients who come in for prostatitis-related care may complain of other problems and therefore return for additional care and procedures. Alternatively, patients with non-specific prostatitis may make additional visits for other nonspecific ailments.

Not surprisingly, a positive association has been found between more severe prostatitis symptoms and higher costs ***(54,62,63)***. Less education and greater pain-related disability scores are also predictors of greater total prostatitis costs ***(54)***. On the basis of data from all 167 men enrolled in the CPC study, Calhoun and colleagues ***(62)*** found that for each unit decrease in the quality of life as measured by the NIH-CPSI, there was a corresponding 25% increase in dollars consumed.

Indirect costs of prostatitis include those of absenteeism, decreased productivity, and personal limitations. An Internet survey of CP/CPPS patients performed by Alexander and Trissel found that 46% of patients had missed some work because of the syndrome ***(44)***. In Calhoun et al.'s CPC study, 26% of patients reported that their prostatitis resulted in absenteeism from work, at an average cost of $551 during the 3 months before entry into the study. This equates to a mean yearly indirect cost of $2,204 per patient. Additionally, 79% of the CPC study participants reported being at least a little less productive while at work and attributed 50% of this productivity loss to their prostatitis symptoms. Twenty-two percent of the men reported having a friend or spouse help them with personal care, medical care, or activities around the house because of their prostatitis. Overall, 49% of the men in the CPC study reported that prostatitis disrupted their leisure time, with a 20% average reduction in the amount of time spent on leisure activities.

6 Conclusion

Prostatitis is a commonly diagnosed condition that is associated with impaired quality of life for sufferers and substantial use of healthcare resources. Many health-related quality of life analyses have highlighted pain intensity as the strongest predictor of quality of life in patients with chronic prostatitis/chronic pelvic pain syndrome, though many other physical and psychological symptoms of the syndrome greatly impact quality of life as well. A great majority of the costs associated with prostatitis are due to individuals with refractory CP/CPPS. An understanding of what causes CP/CPPS and how to treat it will permit more clinically- and cost-effective ways to treat the population of patients with this difficult syndrome.

Additionally, greater research into patient satisfaction with care, quality of life, and economic cost impact should help to increase our understanding of the full burden of CP/CPPS.

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Chapter 6
Antibiotic Therapy in Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Russell Blair Egerdie

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Summary The use of antibiotics in chronic prostatitis/chronic pelvic pain syndrome is widespread and generally accepted. This chapter explores the reasons for this acceptance, presents the evidence based information that would refute this practice, and delineates the areas of confusion that still confound physicians endeavoring to care for these patients.

Keywords Antibiotic; chronic prostatitis; chronic pelvic pain syndrome; CP/CPPS; treatment; therapy.

This may well be the shortest chapter you will read in this book. Antibiotics for the chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)? We all use them, patients expect us to prescribe them; however, is the generalized and rampant prescribing of antibiotics justified in this unfortunate patient group? The jejune answer is no; at this point in time, antibiotic therapy in CP/CPPS has not withstood the test of scientific scrutiny. This chapter will present the limited data supporting this conclusion; however, for very legitimate reasons, it is doubtful that prescribing patterns will, or perhaps should, change in the near future.

CP/CPPS (National Institutes of Health [NIH] category III) is a very important entity to the practicing urologist. Acute bacterial prostatitis (NIH category I), chronic bacterial prostatitis (NIH Category II), and asymptomatic inflammatory prostatitis (NIH category IV) together comprise a negligible percentage of cases compared with the 90% to 95% of the patients that present in category III ***(1)***. It has been reported that approximately 10% to 14% of men are affected by CP/CPPS ***(2)***, translating into an estimated 2 million patient visits per year in the United States ***(3)***.

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Until 1999, the consensus among professionals was that any patient diagnosed with CP/CPPS, either with or without culture confirmed bacterial growth, should be treated with antibiotic therapy ***(4)***. The pioneering work of Meares and Stamey ***(5)*** in the late 1960s on the localization of bacteria in urethritis/chronic prostatitis and the subsequent refinement of the classification system for prostatitis by Drach et al. ***(6)*** led to the publication of several observational papers describing the positive effect of antibiotics on patients classified as having abacterial chronic prostatitis ***(7,8)***. Thus, over the course of 30 years, two generations of urologists were ingrained with the philosophic, rather than scientific, opinion that the appropriate first-line treatment of abacterial chronic prostatitis was antibiotic treatment, and all was well with the world.

The urologic state of affairs in the late 1990s was akin to the situation physicists confronted at the turn of the 19th century. Newtonian physics seemed to have all of the answers and never before had theory and practice seemed so reliable. Despite this congenial confidence, several niggling problems, such as black body radiation, remained. The solution of the black body radiation problem lead to the description of quantum theory, and within two decades, 200 years of classical physics had been scattered to the winds.

The analogy to black body radiation in prostatitis was the nagging awareness that our knowledge of CP/CPPS was based upon a fragile foundation. The seminal studies were observational rather than scientific in design and, more often than not, reflected small numbers of carefully selected cases chosen to popularize the author's point of view. With all other areas of urology embracing the need for randomized, placebo-controlled trials, it became apparent that the classical approach to prostatitis research required reconsideration. The chronic prostatitis equivalent to the quantum leap occurred in 1999.

Three papers were published in 1999 that have challenged and changed our shibboleths. In the first of these papers, Krieger, Nyberg and Nickel, reporting on the work initiated by the NIH in 1995, published the new NIH consensus classification ***(9)***. In this statement, abacterial chronic prostatitis was reclassified as category III: CPPS, and was subdivided into category IIIA (inflammatory) and category IIIB (noninflammatory). This change was important and necessary to reflect the profession's growing recognition that other organs, not just the prostate gland, may be implicated in CPPS and that our understanding of this process is rudimentary at best.

The second essential component was the publication of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) ***(10)***. This 21-item questionnaire was designed and validated for use in both clinical practice as well as research. For the first time a standardized, substantiated instrument was available to the profession, and henceforth all reported results would be subjected to the rigor of comparison to an objective, accepted standardized tool.

The last of the big three addressed deficiencies in prostatitis clinical trials. Reporting in the journal *Urology*, Nickel et al. ***(11)*** presented the accepted new criteria for the design of prostatitis clinical trials. Incorporating the recommendations presented in the previous two papers, which standardized definitions and the classification

of the disease, the entry criteria as well as outcome parameters for clinical trials were defined thereby establishing a solid basis for sound scientific study of the CP/CPPS. The profession was now well positioned to dispassionately and thoroughly appraise the role of antibiotic therapy in CP/CPPS patients. It did not take long for startling new results to appear.

In 2003, Nickel et al. ***(12)*** reported on a Canadian multicenter randomized placebo-controlled trial of levofloxacin in patients diagnosed with CP/CPPS. In this well-designed, but underpowered, study, the patients were treated with either placebo or levofloxacin (500 mg/day) for 6 weeks and were subsequently evaluated 6 weeks after completion of treatment. All patients had experienced pain or discomfort in the pelvic region for at least 3 months, had no cystitis or positive cultures for 12 months before enrolment, and had not received any antibiotic treatment in the month before enrolment. Patient response to treatment was evaluated using the NIH-CPSI, the subjective global assessment, and the patient assessment questionnaire. The study was designed to show statistical significance if 50 subjects were enrolled into each arm.

Unfortunately, only 80 subjects were enrolled (35 in the placebo arm and 45 in the levofloxacin arm). Being underpowered, this study showed no statistical or clinical difference between the two groups despite both groups having mild improvement in symptoms. The question was raised whether a larger study would show a meaningful statistical/clinical difference between the two arms.

The next important report was released in 2004. Under the auspices of The Chronic Prostatitis Collaborative Research Network, 196 men were involved in a randomized, double-blind, 2×2 factorial trial designed to compare 6 weeks of treatment with either ciprofloxacin (500 mg twice a day), tamsulosin (0.4 mg daily), the two drugs together, or placebo ***(13)***. The study was crafted to provide 80% power to detect a 4-point difference in the NIH-CPSI score if 184 patients were recruited. Although all of the four groups showed a slight decrease in the NIH-CPSI score, neither the primary nor secondary outcomes demonstrated any statistically significant difference between the groups.

It might be argued that patient selection in this study was a problem (only tertiary care center referrals were entered into the trial; the mean time from diagnosis was 6.2 years, indicating that many of these patients may be reprobates and may not respond to treatment the way patients with a shorter duration of disease might) or that treatment with antibiotics and/or alpha blockers may need longer than 6 weeks to show results. Still, the fact that neither group showed a significant response when compared with placebo in a well-designed and adequately powered clinical trial was sobering to say the least.

Is that all there is? Are there no well-designed, statistically meaningful studies recorded in the literature that suggest antibiotic use in CP/CPPS is effective and appropriate? Sadly, the answer appears to be no. It was believed for many years that CP/CPPS likely evolved from an initial bacterial infection of the prostate gland. This assumption appears to be ill-founded. In patients with CP/CPPS there seems to be no relationship between the presence or absence of symptoms to the presence or absence of positive bacterial cultures ***(14)***, and the proportion of men with

CP/CPPS with bacteria localized to prostatic secretions is the same as in age-matched controls ***(15)***. The utility of the 4-glass test for the diagnosis of CP/CPPS will be discussed elsewhere in this book; however, these results do call into question the dogma that CP/CPPS develops from a previous bacterial infection of the prostate gland.

As early as 2004 Alexander, writing in *Nature Clinical Practice Urology* ***(3)***, concluded that "…ongoing empiric administration of antimicrobials to men with long-standing CP/CPPS should be abandoned." More recently, an evidence-based analysis of treatment options for CP/CPPS was reported in May 2006 by Dimitrakov et al. ***(16)***. After scrutinizing 10 databases and identifying additional studies by manually searching the bibliographies of the retrieved articles, clinical trials were included for evaluation if they met the following five criteria: "study population defined and classified on the basis of the NIH-CPCRN criteria; administration of a pharmacologic intervention to more than 10 CP/CPPS patients for at least 2 weeks; inclusion of a control group that received placebo, sham intervention, or active pharmacologic or device therapy; use of a randomized, double-blind, parallel-group or crossover design study design; and of validated outcome measures of global status (NIH-CPSI) or individual symptoms (domain scores of the NIH-CPSI)." Only 107 trials were identified that met the criteria and, of these 107, only two studies, previously summarized in this chapter, were applicable to antibiotic treatment of CP/CPPS ***(12,13)***. The somber conclusion of the authors was "there is no effective treatment for this chronic pelvic pain syndrome."

Will urologists stop prescribing antibiotics for patients with CP/CPPS? Of course not. We have little else to offer and, in medicine, the emotional impulse to succor the afflicted has always trumped cold, hard scientific reasoning; patients need to be cared for and we need to demonstrate that caring. To throw up our hands proclaiming "the two randomized clinical trials decree that I have nothing to offer" would appear, and would be, harsh and unfeeling. It would also be simplistic. There is evidence that many patients improve on antibiotics ***(17)***, and there are still some unanswered questions that entreat us, as Benjamin Franklin charged each member of the Continental Congress, to "doubt a little of his own infallibility" on this issue.

As described previously one of the criticisms leveled at the studies reporting the lack of efficacy of antibiotic treatment is that men with refractory, long standing symptoms have introduced selection bias into these tertiary care clinical trials. Because of this it is not yet clear whether or not these results may be translated to patients seen in a community practice setting. This criticism is tempered by Nickel's study ***(12)***, which did involve community based investigators, however, this study was underpowered, the number of patients recruited from tertiary centers compared to the number from the community was not stated, and the proportion of patients entered into the study who had long term, refractory symptoms verses patients who had experienced symptoms for longer than 3 months yet had received no, or minimal, prior treatment was not specified.

It is also possible that in a select subgroup of patients antibiotic therapy may be very appropriate. In a proof of concept study (nonplacebo controlled) Shoskes et al. ***(18)*** proposed that nanobacteria, associated with the production of apatite, may be

implicated in the production of prostatic calculi in younger men with refractory symptoms of CP/CPPS. Men suffering from CPPS that had proved obdurate to treatment were treated with comET. The authors described comET as a mixture of tetracycline 500 mg by mouth at bedtime with nanobacOTC, and a rectal suppository of 1500 mg ethylene diamine tetra acetic acid. NanobacOTC is a proprietary combination of vitamin, C., selenium, ethylene diamine tetra acetic acid, coenzyme Q10, bromelain, grape seed extract, hawthorn berry, quercetin, L-arginine, vitamins B3, B6, and B9, L-lysine, L-ornithine, trypsin, and papain (nanobacOTC is reputed to improve penetration of the stone by the antibiotic). They reported that, of the 16 men entered into the trial, 80% showed at least a 25% reduction on the NIH-CPSI and 53% had 50% or greater improvement.

As in other areas of medicine, combination therapy may yield more promising results. In another interesting proof of concept study, involving only seven patients with Category IIIa disease, Chen et al. ***(19)*** reported on the combination of ciprofloxacin, doxazosin, allopurinol, and biofeedback perineal massage. Patients received 250 mg of ciprofloxacin bid for 2 weeks, and if their symptoms improved, then they were treated for another 4 weeks. If after 2 weeks there was no improvement then the ciprofloxacin was stopped and treatment with allopurinol, doxazosin and biofeedback perineal massage was initiated. All of the seven patients (four received ciprofloxacin alone) demonstrated significant improvement in the NIH-CPSI pain score, and quality of life domains but did not show improvement in the urinary symptoms domain. It is unfortunate that the study did not include an arm involving all four treatments simultaneously.

The inclusion of an antibiotic treatment arm in this study was justified on the basis that current microbiologic techniques may not be sensitive enough to detect a bacterial cause for type IIIa CP, and antibiotics have demonstrated that they influence inflammatory cytokines producing an independent anti-inflammatory response. The antiinflammatory effects of the quinolones and other antibiotics in CP/CPPS deserve further attention. The observed antibiotic response may be related more to modulation of inflammatory cytokines such as tumor necrosis factor, interleukin-6, and interleukin-8 ***(20,21)*** rather than to direct bacterial toxicity. As such the utility of antibiotic therapy in CP/CPPS may be real yet due to an entirely novel mechanism of action.

In addition to these legitimate doubts and considerations the issue is still being confused by the publication of poorly designed trials. Recently, Lee et al. ***(22)*** reported on the efficacy of approximately 6 weeks of gatifloxacin (400 mg/day) treatment for patients they diagnosed with chronic prostatitis. Gatifloxacin was selected because of its activity against Gram-positive, Gram-negative, and anaerobic bacteria. It is also active against atypical uropathogens such as *Mycoplasma pneumoniae, Chlamydia pneumoniae*, as well as ureaplasma urealyticum and is excreted in greater concentrations in prostatic and seminal fluid than the other fluoroquinolones ***(23)***. A total NIH-CPSI score decrease from 20.3 before treatment to 9.9 after treatment was reported in the patients they labeled as having CP; however, the study has significant flaws. There was no placebo control; thus, no true statistical meaning can be ascribed to the results. Equally important was their inappropriate

definition of chronic prostatitis. For inclusion into the study they defined chronic prostatitis as either NIH category II or IIIa and did not indicate what proportion of the total 149 "chronic prostatitis" patients were in each group. There may have been an inordinate number of patients in the category II group and these patients have been shown to respond to antibiotic therapy ***(1)***. These flaws render this study, and many others, anecdotal rather than scientific and must be viewed in this light.

Thus, for all these reasons, room is left for both confusion and for reasonable doubt. This may explain why, as late as 2006, Habermacher et al. ***(1)*** recommended a single 4- to 6-week course of antibiotics as first line treatment for patients with newly diagnosed CP/CPPS. Habermacher echoes the vast majority of the nonacademic private practice urologists. At this juncture, we continue to prescribe a 4- to 6-week course of a quinolone as first-line therapy in patients who present with CP/CPPS because a substantial number of patients do get better with a single course of antibiotic treatment. Are we treating mild cystitis, urethritis, or early CP/CPPS? Who knows? Usually only a midstream urine culture is performed, and well-designed clinical trials have not addressed this group of patients. The two randomized clinical trials, described previously, were limited in scope and have such significant caveat's that the only safe conclusion to be drawn is that previously treated patients, referred to a Tertiary Care center, will not respond to antibiotic monotherapy any better than to placebo. It would be unwise to generalize the observations any further.

With so little to guide us the message is inescapable: only much more determined, dogged, diligent work, inspired by those intrigued with this disease, will render truly meaningful and effective therapeutic results. Fervently do we hope that the day will soon dawn when CP/CPPS syndrome will cease to be "a riddle wrapped in a mystery inside an enigma".

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Chapter 7
Alpha-Blocker Therapy for Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Shaun Wen Huey Lee, Men Long Liong, Kah Hay Yuen, Yee Vonne Liong, and John N. Krieger

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Summary Alpha-blockers represent one of the most common therapies for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The rationale is based on presence of varied receptors in the lower genitourinary tract. Alpha-blockers may work differently for patients with lower urinary tract symptoms related to benign prostatic hyperplasia than for patients with symptoms of CP/CPPS. Starting in the early 1970s, reports suggested that certain patients might benefit from treatment with alpha-blockers. Unfortunately, early nonspecific agents had side-effects that severely limited their clinical utility. More selective alpha-1-blockers offer substantially greater promise. The best studies were double-blinded, randomized clinical trials evaluating tamsulosin, alfuzosin, and terazosin. Current data suggest that treatment-naïve and/or newly diagnosed patients appear more likely to respond than long-term, chronic refractory patients; that longer treatment courses of treatment appear superior to shorter courses; and that less-selective alpha-blockers appear generally superior to more selective agents.

Keywords Prostatitis; alpha blockers.

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1 Introduction

Alpha-blockers represent one of the most common therapies for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) ***(1–3)***. This chapter reviews the rationale for alpha-blockers in patients with symptoms of prostatitis. We demystify confusing terminology and pharmacology, emphasizing that these agents have many common features but also important differences. The alpha-blockers used in urology are not interchangeable from a pharmacological standpoint. These agents may work differently for patients with lower urinary tract symptoms related to benign prostatic hyperplasia (BPH) than for patients with symptoms of CP/CPPS.

The literature supporting use of alpha-blockers for treatment of CP/CPPS is considered from the standpoint of the initial observations and clinical data. These studies resulted in development of high-quality randomized clinical trials. Strengths and limitations of the available data are then used to develop recommendations for alpha-blocker therapy for patients with CP/CPPS.

2 Rationale of Alpha-Blocker Therapy in Patients With CP/CPPS

2.1 Initial Observations

The original rationale for alpha-blocker therapy was based on four clinical observations: 1) Some patients with prostatitis were believed to have dysfunctional voiding and/or bladder outflow obstruction related to prostatic hypertrophy ***(4,5)***; 2) alpha-blockers represent an effective therapy for many patients with voiding dysfunction and bladder-outflow obstruction; 3) some patients with the combination of prostatitis and lower urinary tract symptoms appear to benefit substantially from alpha-blocker therapy ***(5–7)***; and 4) urologists achieved considerable effectivness with alpha-blocker therapy for other indications, demonstrating that these agents are both safe and effective. These observations resulted in empiric use of alpha-blockers for treatment of patients with symptoms of CP/CPPS. Clinically, many patients appeared to improve from this treatment.

3 Alpha-Blocker Pharmacology in the Lower Urinary Tract

Alpha (α) and beta (β) receptor sites can be found in many tissues, such as the blood vessels, spinal cord, prostate, and detrusor muscle. The density of α sites in the genitourinary tract resulted in development of specific pharmacological agents to treat genitourinary problems. Molecular structure analysis has identified two α receptor families, namely $\alpha 1$ (with three subtypes: **a**1a**, a**1b**, a**1d) and $\alpha 2$ (also with three subtypes: **a**2a**,, a** 2b**, a**2c) (8). Alpha-receptors from both families are members

of the G protein-linked family of receptors. Alpha-agonists alter cell activities through various second messenger systems to change cathecolamine levels and induce a broad range of responses. The α1-adrenergic receptors are located predominantly in the postsynaptic cells in smooth muscles, heart, vas deferens, brain, and prostate (Table 1) ***(9–11)***. Improved understanding of alpha-blocker pharmacology and pharmacokinetics resulted in development of agents that are effective in treatment of genitourinary disorders, especially BPH (Table 2). These agents offered potential benefit for patients with other urological disorders, including CP/CPPS. The critical point is that available alpha-blocking agents work at various pharmacological sites and cannot be presumed to be equivalent clinically.

4 Data and Debate

The critical observations supporting use of alpha-blocker therapy for CP/CPPS have become subject to heated debate.

4.1 Bladder Outflow Obstruction and Disordered Voiding in Prostatitis

Perhaps the most controversial statement is that patients with CP/CPPS often have evidence of bladder outflow obstruction and/or dysfunctional voiding that can be

Table 1 Alpha1-Receptor Subtypes

Native[a]	Cloned receptor		Tissue distribution
	Old nomenclature[b]	New nomenclature[c,d]	
a1A	**a**1c	**a**1a	Heart Arterial smooth muscle Prostate Urethral smooth muscle
a1B	**a**1b	**a**1b	Venous smooth muscle Prostate epithelium
a1D	**a**1a, **a**1d, **a**1a/d	**a**1d	Sacral spinal cord Spleen Lung Bladder detrussor muscle Bladder neck

[a]Nomenclature for alpha1-adrenoceptors found naturally in the human.
[b]Molecular cloning techniques have managed to identify three distinct members of α1-adrenoceptor gene products. However, nomenclature to determine native and recombinant adrenoceptors were not consistent, which led to the introduction of a new scheme ***(57)***.
[c]Nomenclature based on the International Union of Basic and Clinical Pharmacology subcommittee on nomenclature for adrenoceptors.
[d]Pharmacological subtype is expressed as capital letters while molecular biological subtype is expressed as small letters.

Table 2 Alpha-Blocking Agents Commonly Used for Treatment of Benign Prostatic Hyperplasia

Category/Agents	Site of action	Main indications	Major side effects
Nonselective			
Phentolamine	Peripheral α receptors	Hypertension	Orthrostatic hypotension
Phenoxybenzamine	Vascular smooth muscle		Reflex tachycardia
Labetolol			Nasal stuffiness
Alpha-difluorom ethylorthinine			Retrograde ejaculation
Selective α1			
Terazosin	Bladder trigone	BPH	Postural hypotension
Doxazosin	Urethra	Hypertension	
Alfuzosin1	Prostatic capsule		
Selective α1a			
Tamsulosin58	Prostate capsule	BPH	Retrograde ejaculation
Selective α1d			
Naftopidil ***(59)***	Bladder smooth muscle	BPH	Postural hypotension

BPH, benign prostatic hyperplasia.

[a]Primary effect of drug, alfuzosin is on the prostatic capsule, resulting in clinical "uroselectivity" ***(60,61)***.

improved by alpha-blocker treatment. Starting in the early 1970s, a number of reports suggested that urodynamic studies could identify patients with chronic prostatitis caused by bladder neck dysfunction and/or obstruction ***(12–21)***. The theory was that dysfunctional voiding resulted in high pressure, turbulent urine flow, intraprostatic reflux of urine into the prostatic parenchyma, or intraprostatic antibody deposition leading to pain and other symptoms ***(16,18,22–26)***. Uncontrolled observations suggested that such patients might benefit substantially from procedures such as endoscopic incision, transurethral resection of the prostate, transtrigonal posterior prostatectomy, or balloon dilation of the prostate ***(17,18,24,27–30)***. Such patients were considered candidates for treatment with alpha-blockers.

Other reports found that alpha-blockers had limited effectiveness because patients with urodynamic evidence of obstruction often responded poorly to treatment with alpha-blocking agents ***(24,28)***. Mayo and associates evaluated the possibility that reports suggesting a high prevalence of obstruction in prostatitis patients might reflect referral of patients to centers interested in urodynamics ***(31)***. They compared findings in 201 men ages 18–50 years who presented to their urodynamics unit with lower tract symptoms with the findings in 123 prostatitis clinic patients. Only 37 (18%) of 201 urodynamics unit patients had pain as a significant symptom and might have been diagnosed as having chronic prostatitis, including 4 (11%) with definite obstruction. Even fewer of the 123 patients with prostatitis had obstruction (definite in 2 [1.6%] and equivocal in 1 [0.8%, $p = 0.03$]). Consistent with these findings, a recent large, randomized clinical trial comparing alpha-blocker with placebo therapy for CP/CPPS found no correlation between clinical response and urodynamic parameters ***(32)***.

Other observations suggest that alpha-blockers might prove effective in treating CP/CPPS by mechanisms other than improvement of urodynamic parameters. Certain alpha-1-blockers work at sites other than the prostate and bladder neck. Such extra-prostatic and extra-bladder neck sites may prove important for the pathophysiology of CP/CPPS32. Mehik and associates ***(33)*** suggest that men with CP/CPPS often have evidence of increased intraprostatic pressure. Their study compared 42 patients with chronic nonbacterial prostatitis with 12 men without urological complaints. Intraprostatic tissue pressure was greater in the patients with prostatitis ($p < 0.001$). The authors hypothesized that this may reflect increased tissue resistance or poor tissue microcirculation. In theory, alpha-blockers might improve these conditions without effecting voiding.

4.2 Uncontrolled and Small Prospective Studies of Alpha-Blocker Therapy for Patients With Symptoms of Chronic Prostatitis

Identification of alpha-adrenergic receptors in the urinary tract raised the possibility that patients with symptoms of prostatitis related to dysfunctional voiding might benefit from pharmacological therapy. Initial studies used agents such as phentolamine ***(34)***, phenoxybenzamine ***(35–37)***, or alpha-difluoromethylornithine ***(36)***. Unfortunately, these nonspecific alpha-blocking agents available in the early 1980s had side-effect profiles that severely limited their clinical effectiveness for treating patients with symptoms of prostatitis ***(38)***.

Subsequently, more selective alpha-1-blocker therapy with fewer side effects was investigated in uncontrolled open label trials ***(39–41)*** and some small randomized prospective studies ***(35,42)***. Beneficial results were reported for alpha-1-blockers in small-controlled trials evaluating terazosin ***(43,44)***, doxazosin ***(45)***, and alfuzosin ***(42)*** (Table 3). These observations were extended in other uncontrolled studies favoring multimodal therapy programs incorporating alpha-blockers in various combinations with antibiotics, antiinflammatory drugs, prostatic massage, antiinflammatory phytotherapy, and neuromuscular agents ***(40,46–48)***. Such observations led multiple investigators to develop reasonably-powered, randomized clinical trials evaluating alpha-blocker therapy ***(49)***.

5 Randomized Clinical Trials of Alpha-Blocker Therapy for CP/CPPS

5.1 Meta-Analysis of Randomized Clinical Trials Using Alpha-Blockers

Four randomized clinical trials met evidence-based criteria for inclusion in a meta-analysis of CP/CPPS therapies (Table 4) ***(32,50–53)***. Pooled estimates from the

Table 3 Uncontrolled and Small Prospective Studies of Alpha-blocker Therapy for Symptoms of Chronic Prostatitis

Author, year, reference	Alpha-blocker (classification)	Design	Active therapy, Follow-up posttherapy	Total participants	Primary outcome
Osborn, 1981 ***(35)***	Phenoxybenzamine (nonselective alpha blocker)	Open label	4 weeks	27	48% of patients improved[a]
De la Rossette, 1992 ***(42)***	Alfuzosin (selective alpha-1)	2-arm multicenter	6 weeks	20	$p = 0.01$
Neal and Moon, 1994 ***(39)***	Terazosin (selective alpha-1)	Open label	4 weeks	25	76% of patients improved[a]
Lacquantti, 1999 ***(44)***	Terazosin (selective alpha-1) or tamsulosin (selective alpha-1 a/d)	3-arm multicenter	8 weeks	18	Terazosin, $p = 0.0002$[b] Tamsulosin, $p = 0.001$[c]
Evligaoglue and Burgot, 2002 ***(45)***	Doxazosin (selective alpha-1)	2-arm, single center	12 weeks	60	$p = 0.001$[d]

[a]Patient response rate was defined as complete symptom resolution.
[b]p value for terazosin versus placebo therapy.
[c]p value for tamsulosin versus placebo therapy.
[d]Primary end point was defined using the change in International Prostate Symptom Score before and after treatment.

randomized clinical trials were created using a random effects model ***(51)***. The authors concluded that these studies provided evidence for efficacy. Overall, pooled relative risk for improvement was 0.57 (95% confidence interval: 0.24–0.91, $p = 0.10$). Although this analysis demonstrated a 42% increase in the likelihood of improvement with alpha-blocker therapy, the amount of improvement was modest.

5.1.1 Limitations

These four studies represent the best current data. In addition, there is a fifth high-quality randomized clinical trial that will soon be completed to add to the body of high-quality data. The studies used three different alpha-blockers. These agents differ in their precise sites and mechanisms of action. Further, there were substantial differences in the study designs, duration of therapy, and in the patient populations evaluated. Such issues, technically termed, "significant heterogeneity," limit the utility of combining the available studies into a single statistical evaluation. Below, we consider the design and results of each study separately.

Table 4 Randomized Clinical Trials of Alpha-Blocker Therapy for Patients With Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Author, year, reference	Alpha-blocker (classification)	Design	Active therapy, Follow-up post-therapy	Total participants	Primary outcome
Nickel, 2004 ***(50)***	Tamsulosin (selective alpha-1a/d)	2-arm multi-center	6 weeks	58 referral patients	$p = 0.04$
Alexander, 2004 ***(52)***	Tamsulosin (selective alpha-1a/d)	4-arm factorial design multi-center	6 weeks	174[a] heavily pretreated, tertiary referral	$p > 0.2$[b]
Mehik, 2003 ***(53)***	Alfuzosin (selective alpha-1)	Three-arm, two centers[c]	6 months, 6 months	66[d]	$p = 0.01$
Pontiari, in progress ***(55)***	Alfuzosin (selective alpha-1)	2-arm multi-center	12 weeks	270 alpha-blocker naïve patients with symptoms for <2 years	In progress
Terazosin, Cheah ***(32,56)***	Non-selective alpha-1	2 arm, single center	14 weeks, 38 weeks	100 newly diagnosed, treatment-naïve patients	$p = 0.03$

[a]This study included 174 evaluable patients, including: 132 treated with placebo, tamsulosin alone, ciprofloxacin alone, or the combination of tamsulosin and ciprofloxacin.
[b]*p* value for tamsulosin versus no tamsulosin therapy.
[c]Randomized clinical trial of alfuzosin or placebo plus "control or standard arm" (sitz bath and anti-inflammatory therapy as needed).
[d]The 66 evaluable patients included 37 in the randomized clinical trial and 29 in the standard/control arm.

5.2 Tamsulosin

Two randomized clinical trials evaluated tamsulosin, an alpha-1a/d subtype-selective blocker, for treating patients with CP/CPPS.

5.2.1 Comparison of Tamsulosin With Placebo Therapy

Nickel and associates ***(50)*** reported a multi-center study comparing tamsulosin to placebo therapy.

5.2.1.1 Population

The authors enrolled 58 patients with CP/CPPS in this multicenter trial. All were younger than 55 years of age and had moderate or severe symptoms. Although the details of previous treatment are not provided, it appears likely that many participants were referred for management of chronic, refractory symptoms.

5.2.1.2 Study Design

This clinical trial was double blind and placebo-controlled. After a 2-week washout period, participants were randomized to receive tamsulosin (0.4 mg daily) or placebo for 6 weeks. Participants were assessed on days 15 and 45 using the NIH-CPSI. The primary end point was the change from baseline NIH-CPSI total score on day 45. Secondary end points were the change from baseline in total NIH-CPSI score on day 15 NIH-CPSI domain scores on days 15 and 45.

5.2.1.3 Results

In this trial, tamsulosin proved superior to placebo. On day 45, patients receiving active therapy had larger decreases in their NIH-CPSI total scores (treatment effect −3.6, $p = 0.04$). Tamsulosin therapy was most effective in participants with higher total NIH-CPSI scores. Comparing the 75th percentile of NIH-CPSI scores at baseline, tamsulosin was more effective than placebo for participants with higher total NIH-CPSI scores (treatment effect −8.3, $p < 0.01$), higher pain domain scores (treatment effect −2.9, $p = 0.02$), higher urinary domain scores (treatment effect −2.3, $p < 0.01$), and worse quality of life domain scores (treatment effect −2.1, $p = 0.02$). The efficacy of tamsulosin increased with time (there was no significant difference between tamsulosin and placebo after 15 days of therapy).

5.2.1.4 Summary

Tamsulosin was superior to placebo in providing symptomatic relief for symptoms of CP/CPPS. Patients did not demonstrate a significant benefit after 2 weeks of therapy, but there was a significant benefit after 6 weeks. The overall benefit of tamsulosin was modest, but men with more severe symptoms at baseline proved significantly more likely to benefit from tamsulosin treatment.

5.2.2 Tamsulosin, Ciprofloxacin, Combination Or Placebo Therapy

One of the most interesting studies was completed by the NIH multicenter Chronic Prostatitis Clinical Research Network ***(49,52)***.

5.2.2.1 Population

This study evaluated a heavily pretreated, tertiary-referral population. The mean duration of prostatitis symptoms was 6.2 years ***(52)***. More than 90% of patients had failed previous therapy with either or both of the agents evaluated.

5.2.2.2 Study Design

This multicenter study used a 2 × 2 factorial design to evaluate four treatments: placebo, tamsulosin hydrochloride (0.4 mg daily), ciprofloxacin (500 mg twice daily), and tamsulosin hydrochloride and ciprofloxacin combined ***(49)***. Because there were relatively few subjects for the chosen design, this study had limited power to evaluate any potential interaction between the treatments. In other words, the study had severely limited ability to determine if one active treatment inhibited or enhanced the other active treatment. Patients receiving combination therapy were included in the comparison of both single active agents to the placebo-treated group.

The primary criterion for response was a 4-point decrease in the NIH-CPSI total score from baseline to 6 weeks. Secondary end points included NIH-CPSI domain scores, a patient-reported global assessment, and mental summary scores on the Medical Outcomes Study 12-Item Short-Form Health Survey. The study was targeted to enroll at least 184 participants.

5.2.2.3 Results

The authors identified important design issues. NIH-CPSI total scores improved significantly in all four treatment groups (by approximately 3 to 6 points), which proved consistent with results in the other randomized clinical trials. These findings support the need for blinding and appropriate placebo therapy groups in CP/CPPS treatment trials. Test results for treatment-by-treatment interaction for the primary end point were considered not significant ($p = 0.075$). Therefore, the primary analysis considered the two main treatment comparisons separately. This study design issue is an important one because the authors might have interpreted this borderline p value as suggesting an interaction between the treatments.

In contrast to the other published randomized clinical trials, this study found no significant difference in the primary outcome for ciprofloxacin versus no ciprofloxacin ($p = 0.15$) or tamsulosin versus no tamsulosin ($p > 0.2$). The best outcome was noted for the 42 participants in the ciprofloxacin only group who experienced an average 6.2 ± 7.3 point decrease in NIH-CPSI compared to a mean decrease of 3.4 ± 5.0 points for the 45 men in the placebo group. The 45 participants treated with tamsulosin alone had an average 4.4 ± 6.3 point decrease in NIH-CPSI. The worst outcomes were noted for the 42 men treated with combination therapy, who had an average 4.1 ± 6.1 point decrease in NIH-CPSI. Treatments also did not differ significantly for any secondary outcome.

5.2.2.4 Summary

This study highlights important issues that should be considered in the design of future clinical trials for CP/CPPS. Although the authors identified no benefit from any treatment, they were careful to emphasize that patients who had received less pretreatment may have responded differently. They also noted that a longer course of therapy may result in better outcomes.

5.3 Alfuzosin

Alfuzosin is an alpha-1a subtype-selective blocker that has been termed "uroselective" because most alpha-1a receptors are found in the prostate ***(54)***. One randomized treatment trial of alfuzosin therapy has been published ***(53)*** and another important trial is currently in progress.

5.3.1 Population

Mehik and associates screened 120 consecutive Finnish men diagnosed with CP/CPPS who presented to two hospital clinics. Participants were offered multiple treatment options.

5.3.2 Study Design

Patients were encouraged to enroll in a double blind placebo-controlled pilot study or to enroll in a "positive control/standard therapy group." They also had the option of receiving treatment without being in a study.

Participants who agreed to the randomized clinical trial received alfuzosin 5 mg twice daily or placebo for 6 months with an additional 6 months of follow-up. Patients who agreed to participate but not to be randomized received "control or standard" therapy consisting of, "traditional hot sitz baths and anti-inflammatories," but no alpha-blockers. No participant in the randomized clinical trial or the standard therapy group received antibiotics or 5-alpha-redutase inhibitors. The outcome measures included changes from baseline in the total and domain scores of the Finnish version of the NIH-CPSI. Improvement was defined as >33% decrease from baseline in NIH-CPSI total and domain scores.

5.3.3 Results

The 66 evaluable participants included 37 in the randomized clinical trial and 29 in the control/standard group. Of the 37 patients in the randomized clinical trial, 17 received alfuzosin therapy and 20 received placebo therapy.

After 6 months of therapy, the alfuzosin group had a greater decrease in total NIH-CPSI score than the placebo and control/standard groups (mean 9.9-, 3.8-, and 4.3-point decreases, respectively, $p = 0.01$). Significantly more improvement occurred in the NIH-CPSI pain domain in the alfuzosin group at 6 months than in the placebo and control/standard groups ($p = 0.01$), but there was no difference in voiding or quality-of-life domains among the three groups.

Of 17 patients in the alfuzosin group, 11 (65%) had >33% improvement in the mean NIH-CPSI total score compared with 5 (25%) of 20 in the placebo group and 9 (32%) of 29 in the control/standard group, respectively ($p = 0.02$). At 12 months, symptom scores in all NIH-CPSI domains decreased in the alfuzosin and placebo groups but not in the control/standard group (mean total NIH-CPSI score 3.5, 0.1, and 5.6 points below baseline, respectively).

5.3.4 Summary

In this study, 6 months of alfuzosin therapy resulted in a modest improvement in the NIH-CPSI, particularly in the pain domain, compared with placebo and standard/traditional treatment. The beneficial effect required several months of treatment and decreased 6 months after treatment was discontinued.

5.3.5 Ongoing Studies

The NIH-Chronic Prostatitis Clinical Research Network is conducting a randomized clinical trial comparing alfuzosin (10 mg daily) to placebo therapy for alpha-blocker naïve patients ***(55)***. Therapy is for 12 weeks. Participants must have CP/CPPS symptoms for less than 2 years, but they may have had considerable previous treatment as long as this treatment did not include alpha-blockers.

The planned enrollment goal is 270 total patients from 11 clinical centers. Currently, this study is progressing well with more than half of the total patients enrolled. This study should provide important information on the benefit this selective alpha-1a blocker for treatment naïve patients.

5.4 Terazosin

Terazosin is considered a nonselective alpha-1-blocker and represents the least selective alpha-blocker evaluated in high-quality randomized clinical trials. Cheah et al. ***(32)*** evaluated terazosin therapy for 100 20- to-50-year-old subjects who met the NIH consensus criteria for CP/CPPS.

5.4.1 Population

Importantly, this study was limited to newly diagnosed patients who had received minimal previous treatment. No participant had received previous alpha-blockers. Thus, this population was substantially different than many of the heavily pretreated, tertiary referral patients evaluated in most studies from North America.

5.4.2 Study Design

This randomized clinical trial had two groups. Subjects were randomized to receive terazosin with dose escalation from 1 to 5 mg daily or placebo for 14 weeks. The primary response criterion was a score of 2 or less ("delighted-to-mostly satisfied") on the NIH-CPSI quality of life item. The secondary response criterion was greater than 50% reduction in NIH-CPSI pain sub-score at 14 weeks. Other outcomes included total and NIH-CPSI domain scores, International Prostate Symptom Score, peak urinary flow rate and post-void residual urine.

5.4.3 Results

5.4.3.1 Initial Response

Terazosin proved superior to placebo in this population of alpha-blocker-naïve patients with CP/CPPS. In the terazosin group 24 (56%) of 43 evaluable subjects met the primary response criterion compared with 14 (36%) of 43 subjects in the placebo group ($p = 0.03$). For the secondary criterion, 26 (60%) of 43 subjects responded in the terazosin group compared with 16 (37%) of 43 in the placebo group ($p = 0.03$). The terazosin group had greater reductions ($p < 0.05$) in NIH-CPSI total score, individual domain scores and International Prostate Symptom Score than the placebo group. There was no difference in peak urinary flow rate or post-void residual between responders and nonresponders. In the terazosin group 18 patients (42%) had side effects compared to 9 (21%) in the placebo group ($p = 0.04$), as one might predict.

5.4.3.2 Long-Term Results

During follow-up of this series, nonresponders and responders who subsequently relapsed were treated with terazosin or other medications (open label) ***(56)***. The authors used the same criterion for response as the initial report (a score of 0 to 2 on the NIH-CPSI quality-of-life item.) Long-term response was evaluated after a median of 38 weeks (range 34–42), regardless of any additional treatment. A durable response was defined as an initial response (after the initial 14-week treatment period) without additional treatment. Long-term responses were noted in 23 (56%)

of 41 assessable subjects treated with terazosin initially compared with 12 (32%) of 38 assessable subjects treated with placebo ($p = 0.03$). Of nonresponders and initial responders who relapsed, 7 (41%) of 17 subjects responded to terazosin compared with 7 (21%) of 34 given other treatments ($p = 0.12$). Durable responses occurred in 18 (44%) of the 41 assessable patients treated with terazosin initially compared to 6 (16%) of 38 treated with placebo initially ($p = 0.01$).

5.5 Summary

Newly diagnosed, alpha-blocker naïve patients who received 14 weeks of terazosin were more likely to have initial, long-term, and durable responses than those treated with placebo.

6 Current Role of Alpha-Blocker Therapy and Clinical Questions

Alpha-blockers represent one of the few treatments for CP/CPPS supported by high-quality clinical trial data. Clinically, many patients respond to these agents.

Current data support the following recommendations and conclusions:

1. Critical study design outcomes and issues have been resolved, facilitating development of additional high-quality treatment studies.
2. Treatment-naïve and/or newly diagnosed patients appear more likely to respond than long-term, chronic refractory patients.
3. Longer courses of treatment (12 weeks to 6 months) appear superior to shorter courses of treatment (6 weeks).
4. Less-selective alpha-blockers appear generally superior to more selective agents.

The five major issues that require resolution are as follows:

1. We need to define the precise sites and receptors responsible for the benefit of alpha-blockers in CP/CPPS. Such sites may be in the prostate, the bladder, spinal cord, or other anatomic locations. These sites and receptors may well differ from the critical sites and receptors responsible for lower urinary tract symptoms related to benign prostatic hyperplasia.
2. We need to define the optimal alpha-blocker and duration of treatment.
3. We need to define whether alpha-blockers should be used as monotherapy or as part of a combination of treatments.
4. We need to define the optimal time to employ alpha-blockers in the natural history of CP/CPPS. Should these agents be used as initial therapy, as second-line treatment perhaps after antimicrobial or other therapy, or after multiple courses of other treatment agents?

5. Should alpha-blockers be prescribed as one component of "combination therapy" with other agents or nonpharmacological treatments?

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Chapter 8
Phytotherapy and the Prostatitis Syndromes

Daniel A. Shoskes

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Summary Given the lack of proven efficacy of conventional therapies, it is not surprising that patients have turned with increasing frequency to phytotherapy and other alternative treatments. Although alternative therapies are plentiful, few have been subjected to scientific scrutiny and prospective controlled clinical trials. This chapter will cover therapies commonly used in prostatitis patients and focus in detail on those with published data. These treatments include zinc, cernilton (bee pollen), quercetin, and saw palmetto. Complementary therapies may indeed have much to offer patients, particularly those with chronic degenerative conditions in which allopathic therapies have proven less successful. Alternative therapies, however, require the same scientific criteria for validation and acceptance as do conventional medical therapies.

Keywords Prostatitis; quercetin; zinc; bioflavonoids.

1 Introduction

The prostatitis syndromes are some of the most prevalent conditions in urology but also the most poorly understood. Although little controversy exists over the therapy for documented acute or chronic bacterial infections, most patients fall into the

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"nonbacterial" or "prostatodynia" group (National Institutes of Health category III). The etiology, natural history, and appropriate therapy for these patients are very unclear. Patient and physician dissatisfaction with these syndromes is high, making it an area ripe for patient interest in nontraditional and alternative therapies.

Alternative medical therapies in general and herbal therapies in particular are popular in North America and, in Europe and Asia, they are often the treatment of choice for chronic medical conditions. In the United States, Congress in 1994 removed such therapies from the jurisdiction of the Food and Drug Administration as long as no claims for specific efficacy for medical illnesses are stated. This act of corporate largesse has had two unintended consequences: 1) there is no oversight of quality control on ingredients sold as herbal products (up to two-thirds don't have the ingredients stated on the label according to consumer watchdog studies) and 2) patients searching for products for their specific conditions are met with completely meaningless descriptions such as "supports prostate health" but can't tell if the product may have efficacy for BPH, prostatitis or prostate cancer. As further consequences, pharmacokinetic and bioavailability data are lacking, interactions with other drugs (natural or synthetic) are unknown, and there is no ongoing data accumulation of adverse events. Nevertheless, phytotherapy may provide several unique benefits. They may provide unique mechanisms of action unavailable through traditional pharmaceuticals or available only at the cost of considerable side effects (e.g., Cox-2 inhibitors). They are often much less expensive than pharmaceuticals, although their cost is usually not covered by drug plans. Perhaps most important of all, there is very high patient acceptance. It is the rare patient indeed who responds negatively to a physician's suggestion of using an herbal based product, particularly when there is published data to support its use.

This chapter will review where phytotherapeutic agents may play a helpful role in the different prostatitis syndromes, either alone or as part of a multimodal regimen. Although published literature is scarce, emphasis will be placed on therapies with some clinical evidence and scientific rationale for use.

2 Category I (Acute Prostatitis)

Category I prostatitis is well understood, typically responds to antibiotics therapy and, through sepsis and the cytokine release syndrome, can be fatal. As such, patients should be discouraged from pursuing alternate forms of therapy, be they natural products with "antibacterial activity" or complementary therapies that may interact with antibiotics to lower tissue levels or block their effects ***(1)***. For example, quinolone antibiotics exert their primary antibacterial effect by binding to the Gyr A subunit of the DNA gyrase holoenzyme, which then inhibits supercoiling ***(2)***. The bioflavonoids rutin and quercetin (discussed below), can bind to these same receptors but have very weak antibacterial action ***(3)***. Therefore, they could theoretically act as competitive inhibitors to quinolone antibiotics and interfere with their action.

3 Category II (Chronic Bacterial Prostatitis)

The mainstay of therapy for category II prostatitis is antibiotics. Therefore, the same caveats mentioned for antibiotic interactions in category I also apply. In addition, chronic use over weeks or months can lead to alterations in gastrointestinal flora. These changes can lead to gastrointestinal (GI) upset and chronic diarrhea. Probiotics are active bacteria that form the normal microbiota of the GI tract and can be given orally to prevent and treat antibiotic associated diarrhea ***(4)***. Both lactobacilli and, *S. boulardi* have been shown in randomized placebo controlled trials to be helpful in this setting ***(5)***. Although never studied specifically in prostatitis, patients who go on prolonged courses of antibiotics should be informed that probiotics may help to reduce the risk and severity of antibiotic side effects.

Zinc is a known component of prostatic fluid and has an antibacterial effect. Prostatic fluid levels of zinc are markedly reduced in men with category II prostatitis ***(6)***, and this reduction is unrelated to circulating zinc levels, nor does it increase with exogenous oral administration ***(7)***. Direct injection of zinc into the prostate in one study was no better than prostate massage and antibiotics alone ***(8)***. In a primate model, zinc levels in the prostate started as normal, decreased during *Escherichia coli* infection and then returned to normal after resolution ***(9)***, further suggesting that these zinc changes were an effect rather than a cause. On the basis of these data, the use of supplemental zinc in men with category II prostatitis is not supported.

Cranberry juice is touted as effective for urinary tract infections, although randomized placebo controlled trials are lacking ***(10)***. There is evidence that cranberry juice may decrease adherence of bacteria to uroepithelial cells ***(11)***; however, there is no evidence that this would have a clinically relevant effect in male urinary tract infection or prostatitis ***(12)***. Conversely, because cranberry juice can acidify urine, its use may actually exacerbate the symptoms of men with uroepithelial inflammation. Therefore, cranberry juice is not recommended for category II prostatitis therapy or prevention.

4 Category III (Chronic Pelvic Pain Syndrome [CPPS])

CPPS is both the most common form of prostatitis and the most cryptic. The etiology and pathophysiology is controversial and, in fact, the disorder likely represents different underlying etiologies that produce a common symptom complex. Some patients with CPPS may have a true bacterial infection, which may be missed because cultures are not properly done ***(13)***, because difficult-to-culture organisms are not tested (e.g., Ureaplasma, Mycoplasma), or because the bacteria may not be identifiable by current culture techniques ***(14)***. In the absence of infection, there is evidence for an inflammatory or autoimmune component to CPPS. Even in the absence of visible white blood cells, the expressed prostatic secretions (EPS), and semen of men with CPPS have increased levels of inflammatory cytokine ***(15)*** and

oxidative stress ***(16)***. Furthermore, symptomatic response to antibiotics in CPPS patients may be caused by direct antiinflammatory effects of these drugs rather than their antimicrobial effects ***(17)***. Finally, much of the pain of CPPS is likely related to pelvic muscle spasm, which may be secondary to infective or inflammatory conditions mentioned above or may be the primary problem itself in the absence of any prostatic pathology ***(18)***. Pelvic muscle spasm can lead to chronic intermittent hypoxia, which may be improved by antioxidant therapy ***(19)***. It would be expected therefore that the greatest potential role for phytotherapy in CPPS would be for antioxidant and anti-inflammatory effects.

5 Phytotherapy for CPPS

5.1 Saw Palmetto

Saw Palmetto is the most commonly used herbal agent for lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia and, indeed, some of the clinical studies with entry criteria based upon symptoms likely included patients with CPPS ***(20)***. Although commercially promoted as "herbal Proscar," it is unclear whether the beneficial effects are from dihydrotestosterone blockade, alpha-1 receptor blockade, or some other unknown mechanism ***(21)***. The efficacy of Saw Palmetto for treating LUTS is not firmly established ***(22)***. A lipido-sterolic extract of Serenoa repens, Permixon, is popular in Europe and has the most published data supporting efficacy ***(23)***.

In a prospective randomized (but not placebo-controlled) trial comparing Saw Palmetto with finasteride in men with CPPS, there was no improvement in symptoms after 12 months in the Saw Palmetto arm ***(24)***. A randomized, placebo-controlled study using Permixon in 61 patients by Reissigl et al. found mild improvement in CPSI scores in 75% of patients and moderate to marked improvement in 55% of patients on active treatment versus 20% and 16% of control patients, respectively. This study was presented at the 2004 American Urological Association meeting and as of early 2007 has not been published.

5.2 Pollen Extracts/Cernilton

Cernilton, an extract of bee pollen, has been used in prostatic conditions for its presumed antiinflammatory and antiandrogenic effects. In a small open-label study, 13 of 15 patients reported symptomatic improvement ***(25)***. In a larger open-label study, 90 patients received one tablet of Cernilton N three times a day for 6 months ***(26)***. Patients with "complicating factors" (e.g., prostatic calculi, urethral stricture, bladder neck sclerosis) had minimal response, with only 1 of 18 showing improvement. In the "uncomplicated" patients, however, 36% were cured of their symptoms and

42% improved. Symptomatic improvement was typically associated with improved uroflow parameters, reduced inflammation and a decrease in complement C3/coeruloplasmin in the ejaculate.

More recently, a pollen extract, Prostat/Poltit, was evaluated in a 6-month prospective, randomized placebo controlled trial ***(27)***. Of 30 patients treated with pollen extract, 6 were free of symptoms and 16 were "clinically improved." In the placebo group, 10 of 28 patients were clinically improved and none were symptom free. The primary limitation of the study was lack of a validated outcome measure.

5.3 Quercetin

The bioflavonoids are a family of polyphenolic molecules found in a variety of plants that have significant antioxidant and antiinflammatory properties ***(28)***. Quercetin is a member of this family found in red wine, green tea, and onions (Fig. 1) ***(29)***. It is a potent free oxygen scavenger ***(30)***, antioxidant ***(31)***, and anti-inflammatory agent ***(32)***. It reduces inflammation by inhibiting the production of cytokines such as interleukin-6 ***(33)***, interleukin-8 ***(34)***, and tumor necrosis factor ***(35)*** through the inhibition of the promoter nuclear factor-kB ***(36)***. Interestingly, these cytokines are elevated in the semen and prostate fluid of men with CPPS ***(37)***. Absorption of dietary quercetin is variable, and dependent on gut flora ***(38)***.

For these reasons, quercetin had theoretical benefits for patients with an ongoing inflammatory or ischemic process, which may underlie CPPS. In addition, because CPPS patients often avoid foods rich in flavanoids (green tea [caffeine], red wine [alcohol]), they may have an actual dietary deficiency of quercetin. In a preliminary small, open-label study, 500 mg of quercetin administered twice daily gave significant symptomatic improvement to most patients, particularly those with negative EPS cultures ***(39)***. This was followed by a prospective, double-blind, placebo-controlled trial of 500 mg of quercetin administered twice daily for 4 weeks, using the NIH-CPSI as the primary endpoint ***(40)***. Patients taking placebo had a mean improvement in NIH-CPSI from 20.2 to 18.8; those taking quercetin had a mean

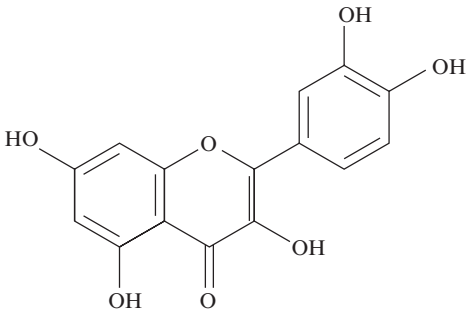

Fig. 1 Chemical structure of quercetin

improvement from 21.0 to 13.1 ($p = 0.003$). Twenty percent of patients taking placebo and 67% of patients taking the bioflavonoid had an improvement of symptoms of at least 25%. This 25% improvement threshold is associated with patient perception of being improved following therapy. A third group of patients received Prosta-Q (Farr Labs, El Segundo, CA), a commercial formulation containing quercetin with bromelain and papain, which are digestive enzymes known to increase the intestinal absorption of quercetin. In this group, 82% of the patients showed a significant improvement in symptoms.

Several mechanisms may contribute to the beneficial effects of quercetin in CPPS. CPPS is associated with elevated oxidative stress in EPS and semen ***(41)*** and patients who improve with quercetin have a reduction in oxidative stress metabolite F2-isoprostane in their EPS ***(16)***. Furthermore, quercetin therapy reduces inflammation as measured by prostaglandin E2 levels in EPS and increases the levels of prostatic beta-endorphins ***(42)***. In an attempt to explain why some patients respond to quercetin therapy and others do not, blood from CPPS patients treated with quercetin was analyzed for cytokine polymorphisms. All 11 of the 28 patients treated with the anti-inflammatory quercetin in whom treatment failed had the low tumor necrosis factor genotype versus 29.4% of those in whom treatment succeeded ($p = 0.0003$). Similarly men with quercetin treatment failure were much less likely

Table 1 Summary of Phytotherapy for Prostatitis Syndromes

Category	Agent	Effect	Evidence
II	Probiotics	Reduce incidence of diarrhea in patients on prolonged courses of antibiotics	Randomized placebo-controlled trial
	Zinc	Levels are low in patients but exogenous administration does not raise levels and does not improve symptoms	
	Cranberry juice	Reduction in bacterial adherence to bladder wall. No evidence of benefit in prostatitis	
III	Saw Palmetto	No change in prostatitis symptoms at 1 year	Prospective randomized trial, not placebo controlled
	Permixon	Reduction in symptoms	Two randomized placebo controlled trials, so far only published in abstract form
	Quercetin	Reduction in symptoms after 4 weeks therapy. Reduction in oxidative stress and PGE2 in prostate fluid.	Randomized placebo controlled trial. CPSI as outcome measure
	Cernilton/Pollen Extract	Reduction in symptoms	Randomized placebo controlled trial. Nonvalidated outcome measure

to have the low interleukin-10 genotype than those with treatment success (9.1% vs. 47.1%, $p = 0.04$). Therefore, men with a "low inflammation" phenotype were less likely to improve with quercetin. Finally, quercetin does have weak antibacterial and antifungal properties which might conceivably play a role in CPPS ***(43)***.

Side effects with quercetin therapy are rare. Some patients experience nausea if taken on an empty stomach. Some patients have reported transient joint pain when quercetin is taken at high doses. Orange pigment in some preparations may show up in semen, and patients can be reassured that this is the dye and not an infection. Because quercetin binds to the DNA gyrase site on *Escherichia coli*, where quinolone antibiotics bind, quercetin could theoretically interfere with quinolone antibiotics, so the two should not be used together ***(44)***. Quercetin may however be safely be combined with nonquinolone antibiotics.

In men with CPPS who have negative cultures, I will typically use quercetin at 500 mg two to three times per day (Table 1). Some patients note improvement in symptoms within days, but I recommend at least a 6-wk trial. If improvement begins within 6 weeks, symptoms usually continue to improve further out to 3 months. I will often combine quercetin with bromelain and papain to help enhance absorption (Prosta-Q, Farr Labs) or additionally combine with bee pollen (Q-Urol, Farr Labs). In men with voiding symptoms, I will usually combine quercetin with an alpha blocker. In patients with pelvic muscle spasm, I will combine quercetin with pharmacotherapy (e.g., nortriptyline) or pelvic muscle physical therapy, in an attempt to treat the hypoxic skeletal muscles.

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Chapter 9
Neuromuscular and Psychoactive Treatments for Chronic Prostatitis

Michel Pontari

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Summary Once the traditional first-line therapies for chronic prostatitis/chronic pelvic pain Syndrome (CP/CPPS) consisting of antibiotics, alpha-blockers, and anti-inflammatory medications fail, there are several other treatments to consider. One of the findings in men with CP/CPPS is alterations in the nervous system that are found in other chronic pain syndromes and result in hyperexcitability of the central nervous system and neuropathic pain. Medications used to treat such pain include tricyclic and nontricyclic antidepressants and anticonvulsants. These men are also found to have increased tone in the muscles of the pelvic floor and external urethral sphincter. Medications used to treat this spasticity include those used in back pain with spasm, such as cyclobenzaprine and Tizanidine. Medications such as montelukast, which is used to treat interstitial cystitis, may also be useful in men with CP/CPPS. Finally, surgical procedures such as bladder neck incision or interStim implantation may also have a role in the treatment of these patients.

Keywords Neuropathic pain; tricyclic antidepressants; pregabalin; tizanidine; cyclobenzaprine; bladder neck incision; neuromodulation; pelvic floor spasticity.

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1 Introduction

The pain from chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) has in the past been attributed to ongoing, undiagnosed infection in the prostate. Multiple courses of antibiotics were administered an attempt to give large enough doses to eradicate the suspected pathogen. Although antibiotics have a role in the early treatment of CP/CPPS, other treatments usually are needed. Second-line therapy consists of alpha-adrenergic antagonists and antiinflammatory medications. However, these medications often are not sufficient to significantly control symptoms. Once the traditional first-line therapies of antibiotics, alpha-blockers, and antiinflammatory medications fail, there are several other medications to consider. These medications aim to treat neuropathic pain and the resultant spasticity of skeletal muscles in the pelvic floor. In addition to medications, neuromodulation techniques target the same areas. This chapter examines the background for using such interventions and discusses use of these medications and devices.

2 Involvement of the Nervous System in CP/CPPS

The term prostatitis implies inflammation involving the prostate. True et al. ***(1)*** found prostatic inflammation in only 33% of patients with CP/CPPS who underwent transperineal prostate biopsy. Although this study is limited because it took perineal biopsies and because the peripheral zone may not be accessed as it is for transrectal biopsies, it nonetheless raises the question of whether the prostate is even involved in the symptoms of CP/CPPS. Even when inflammation is present in the prostate based on examining seminal plasma, expressed prostatic secretions, and/or postprostate massage urine (VB3), there is no correlation with symptoms nor are the amounts of inflammation different from those found in age matched men without symptoms of CP/CPPS ***(2,3)***.

Pain is the symptom that separates men with CP/CPPS from other men with voiding symptoms alone, such as with lower urinary tract symptoms/benign prostatic hyperplasia (LUTS/BPH) ***(4)***. This indicates some neurologic involvement, either on a local level or in the central nervous system (CNS). The nervous system itself may be the source of the symptoms. CP/CPPS has the hallmarks of a chronic pain syndrome ***(4)***. CPPS is characterized by sensitization of the CNS, particularly in the dorsal horn of the spinal cord, involved in sensation and transmission of pain. Biochemical changes, including inflammation in the nerves, lead to hyperexcitability. Lower thresholds are required for pain transmission. Individuals may experience allodynia, in which a stimulus that is normally not painful produces pain, or hyperalgesia in which pain is experienced in the absence of any stimulus at all. There is evidence in animal models as well as a growing body of evidence in humans that these conditions exist in patients with CP/CPPS.

Experimental evidence for central remodeling is provided by the finding that chemical irritation of rat prostate and bladder causes c-fos expression at spinal cord

levels L6 and S1 along with plasma extravasation at the identical L6 and S1 dermatomes, underscoring the overlap of afferent nerve fiber distribution ***(5)***. One of the hallmarks of such remodeling, or 'windup," is neurogenic inflammation. In the Wistar rat model of prostatitis, an increased density of nerve fibers, the sensory neuropeptide calcitonin gene-related peptide, and evidence of progressive mast cell degranulation are noted at progressive time points ***(6)***. One of the products released from activated mast cells is nerve growth factor, or nerve growth factor (NGF) ***(7)***.

The importance of NGF is that it is one of the few factors that correlates with the pain in CP/CPPS ***(8)***. NGF is a neurotrophin that has been found to play a role in regulation of nociceptive nerves and as a mediator and amplifier of neurogenic inflammation. NGF is a survival factor for both sympathetic and sensory neurons during development ***(9)***. Most sensory neurons cease to rely on NGF in the postnatal period ***(10)***, but many small diameter peptide containing sensory nerves in the adult have high affinity NGF receptors and retrograde transport NGF from their target tissues ***(11)***. The concentrations of NGF in damaged or inflamed tissue have been shown to increase many fold above normal ***(12)***. NGF regulates the sensitivity of adult sensory neurons to capsaicin, which excites C-mechano heat receptors ***(13)***. These C fibers are sensory nerves associated with pain transmission and also innervate mast cells ***(7)***.

There is evidence that artificially increased concentrations of NGF in a peripheral target can also sensitize central neurons to afferent barrages from that target ***(9)***. This can lead to sensitization of central neurons by enhanced neurotransmission mediated by the NMDA receptor that produces long lasting depolarizations ***(14)***. Given the role of NGF in neurogenic inflammation and nociception, its correlation with pain in CPPS supports the idea that neurogenic inflammation is involved in the pathogenesis of the symptoms of CP/CPPS.

The presence of central sensitization in patients with CPPS was assessed by Yang et al. ***(15)***, who compared thermal algometry in men with CPPS with asymptomatic controls. Sensitivity to noxious heat stimuli is thought to be a reflection of central sensitization The men with CPPS reported a higher visual analog scale to short bursts of noxious heat stimuli to the perineum but no difference to the anterior thigh. Thus, these patients have altered sensation in the perineum compared with controls. This finding is similar to other chronic pain syndromes such as reflex sympathetic dystrophy and fibromyalgia, where patients also have heightened responses to noxious heat stimuli in areas of chronic pain compared with controls. Data to further support a neurologic hypothesis are given by Zermann et al. ***(16)***. They found significant abnormalities in the coordination of voiding and activity in the pelvic floor/external urethral sphincter in more than 80% of their men with symptoms of pelvic pain. This kind of dysfunction is classically found in patients with suprasacral spinal cord lesions, such as patients with a full spinal cord injury, or men with spinal cord plaques from multiple sclerosis. This raises the question as to whether these men have a subclinical neural injury in the spinal cord that would contribute to such dyssynergy and, thus pelvic pain neurostimulation ***(17)***, supporting the idea that whatever the inciting insult, there is a common pathway to nerve dysfunction in these patients. Finally, In the National Institutes of Health (NIH) cohort study, a

history of neurologic disease was almost five times more likely in the cases compared with the controls. The defining symptom in patients with CPPS is pain, which indicates some neurologic involvement, either locally or centrally. In the NIH cohort, the symptom that most contributed to the difference in neurologic disease was numbness and tingling in the limbs ***(18)***. Although migraine headaches were common in the cases, they were not significantly different than controls. Also significant was a history of vertebral disc disease/surgery. Thus, subclinical disc disease or injury could be contributing to pelvic pain.

3 Treatment of Neuropathic Pain in Men With CP/CPPS

3.1 Tricyclic Antidepressants

Tricyclic antidepressant medications (TCAs) are widely used for neuropathic pain ***(19,20)***. Tricyclics are thought to block pain by inhibiting the central neuronal reuptake of norepinephrine and serotonin, potentiating the inhibitory effect of these substances on central pain processing receptors ***(21,22)***. There is some literature suggesting that TCAs that block serotonin preferentially over norepinephrine are better analgesics ***(23)***. Other studies have shown no difference ***(24)***. As with other chronic pain syndromes, some patients with CPPS report that their pain is made worse by stress. In animal models, both serotonin and norepinephrine are involved in mediating stress-induced pain ***(25)***. Other mechanisms of action for the TCAs include NMDA receptor antagonism and blocking sodium-channels ***(26)***.

The most commonly studied tricyclic antidepressant medication has been amitriptyline ***(27,28)***. The major limitation of amitriptyline is side effects, including sedation and anticholinergic effects. The TCA nortriptyline is much less potent than amitriptyline in inhibiting serotonin reuptake but has a greater effect, inhibiting the reuptake of norepinephrine, and also produces less sedation and other side effects ***(23)***. In a randomized double-blind trial, nortriptyline was found to provide equivalent analgesic benefits in patients with postherpetic neuralgia when directly compared with amitriptyline but was better tolerated ***(29)***. More recent reviews of treatment of neuropathic pain have suggested nortriptyline as a first-line therapy when using TCAs given its favorable side effect profile ***(30)***.Currently, we use nortriptyline as our first-line TCA because it may produce less sedation than amitriptyline and many of our patients are relatively young and working. Starting doses are 10 mg by mouth at the hour of sleep qhs working up to a maximum of 75–100 mg qhs. Other side effects include anticholinergic side effects such as dry mouth; they may have a beneficial effect on urinary frequency.

It is important to tell men with CP/CPPS before they fill their prescriptions that these medications are commonly used as antidepressants but that is not the reason that they are being prescribed. Patients may have anxiety if they think their physician is prescribing these either for depression or may get the idea that the prescribing physician thinks the symptoms are psychosomatic in origin. The doses used to

treat neuropathic pain are usually significantly lower than those used to treat depression and I usually mention this to my patients.

3.2 Non-TCAs

Given some evidence that so-called balanced drugs, which block both serotonin and norepinephrine reuptake, do not have better results than relatively selective drugs that selectively inhibit norepinephrine reuptake and have significantly greater side effects ***(19)***, others have used medications such as buproprion to treat neuropathic pain. Buproprion is a second-generation, non-TCA that is a relatively specific inhibitor of neuronal norepinephrine reuptake. This medication has been shown to be effective in nondepressed patients with low back pain ***(31)*** and neuropathic pain in both open-label ***(32)*** and randomized placebo-controlled trials ***(33)***. Buproprion has been shown to be well tolerated and effective in patients with neuropathic pain in whom traditional tricyclic medications were either not tolerated ***(34)*** or effective ***(33)***.

3.3 Anticonvulsants

Gabapentin and pregabalin are anticonvulsants that are also effective in treating neuropathic pain. Pregabalin has recently been approved for the treatment of postherpetic neuralgia (PHN) and diabetic neuropathy (DN). Although structurally related to GABA, they do not act at GABA receptors and does not act in a physiologically similar way to GABA ***(35)***. They bind to the alpha-2-delta subunit of voltage gated calcium channels, selectively attenuating depolarization-induced calcium in flux into neurons via presynaptic channels and reducing the release of several excitatory neurotransmitters including glutamate, noradrenaline, and substance P ***(36–39)***. Within the dorsal root ganglion, increased expression of the a-2 delta subunit of voltage gated calcium channels also correlates with the onset of and duration of allodynia ***(40)***. One of the advantages of using Pregabalin is that its binding affinity to the alpha-2-delta subunit of voltage gated calcium channels is 6-fold greater than that of Gabapentin ***(41)***. Therefore, a lower does of pregabalin can be used to achieve efficacy, resulting in fewer side effects.

Pregabalin has been reported to significantly improve pain scores compared with placebo in patients with PHN ***(41,42)***, the DN study ***(43)***, and fibromyalgia ***(44)***. As an example of the degree of its efficacy, in the Dworkin study ***(42)***, the primary efficacy measure was the mean of the last seven daily pain ratings. Pregabalin-treated patients had greater decreases in pain than patients treated with placebo with endpoint mean scores (3.60 vs. 5.29, $p = 0.0001$). This study also used the McGill pain questionnaire and significant improvement on the total, sensory, and affective pain scores was also found. As a secondary measure, sleep also

improved in patients treated with pregabalin compared with placebo. Similar results were also found in the fibromyalgia study ***(42)***, in which end mean pain scores showed a decrease of −0.93 difference for pregabalin compared with placebo and significantly more patients in this group had ≥50% improvement in pain at the end point (29% vs.13% in the placebo group; $p = 0.003$). Again, secondary measures including sleep quality, fatigue, and global measures of change were significantly improved over the placebo group.

The dose of pregabalin used has varied in different studies. In assessing PHN, Dworkin et al. ***(42)*** used doss of 300 mg per day in three divided doses or 600 mg per day in three doses. The decision on which dose to use was made based on creatinine clearance; patients with a clearance of <60 mL/min received 100 mg by mouth three times daily; those with a clearance >60 mL/min received 200 mg by mouth three times daily. Pregabalin is renally excreted and significant impairment of renal function could lead to higher blood levels ***(17)***. Sabatowski et al. ***(41)*** used doses of 150 and 300 mg by mouth in three divided doses in a random fashion. The DN study ***(43)*** compared 300 mg per day as 100 mg by mouth three times per day versus placebo; no dose escalation was used for this trial. Pregabalin has been used in a twice-per-day dosing ***(45)***. The efficacy appears to be dose dependent ***(46)***.

Just as the efficacy is dose related ***(46)***, so too are completion rates in the studies and side effects. Double-blind study completion rates are reported at 88% and 79% with 150 mg and 300 mg per day of pregabalin versus 75% placebo ***(40)*** and reduced to 65% for the 600-mg dose ***(41)*** in the studies on PHN. In the diabetic neuropathy study at dose of 300 mg per day, the completion rate was 86% compared with 89% of placebo patients in this trial ***(42)***. The main side effects seen in clinical studies include dizziness, somnolence, peripheral edema, headache, dry mouth, and diarrhea. The side effects of dizziness, somnolence, and peripheral edema are also dose related, but with little difference between the 300 mg and 600 mg per day in a three-times-per-day dosing ***(46)***.

Pregabalin is approved for use by the European Union for neuropathic pain, including PHN and diabetic neuropathy, at doses of 150–600 mg as either two or three doses per day. The dose can be titrated up from 150 per day to 300 mg per day after 3–7 d. Currently, we start 50 mg by mouth three times per day and go up to 100 after 1 wk. The dose can then be increased to 600 mg per day if needed after an additional 7 d ***(46)***. In the study on fibromyalgia, which is a chronic pain syndrome similar in many ways to CP/CPPS, a dose of 450 mg was needed to achieve efficacy ***(44)***. Therefore, before increasing the dose to 600 mg, a dose escalation up to 450 mg should be tried first. If patients have side effects, they should be titrated down to the lowest previous dose that was well tolerated. From there, small 50-mg increases in dose may be tried to better treat symptoms but avoid side effects. The drug should not be stopped abruptly, but should be tapered over at least a 1-wk period. The effects of pregabalin may be observed very quickly. In trials, the analgesic effects of pregabalin are noted in the first week ***(41,43)*** and as early as the second day ***(42)***. There was no appreciable change in the response from week 1–2 to week 8 in two studies ***(41,43)*** and weeks 3 to 8 in another study ***(42)***, indicating that the maximum effect of the drug will be seen soon after starting the drug or increasing the dose.

Dizziness, somnolence, and peripheral edema of mild-to-moderate intensity are the most frequently observed adverse events. Pregabalin is not metabolized by the liver, does not affect the cytochrome P450 system, nor is it bound to plasma protein and therefore does not have drug–drug interactions from these mechanisms ***(35)***. No specific drug interactions have been reported. Before use, a creatinine clearance can be calculated for those patients with an elevated creatinine. A creatinine clearance less than 30 mL/min should exclude patients from receiving the medication. An additional precaution relates to reproductive toxicity. The package insert recommends that men being treated with Pregabalin who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain.

3.4 Tramadol

Tramadol is a weak opioid and a mixed serotonin-noradrenaline reuptake inhibitor that has shown efficacy in diabetic neuropathy ***(47)*** at doses of 50 mg by mouth four times daily. Recent evidence also suggests that it works at both sodium and potassium channels ***(48,49)***. Side effects include headache, constipation, and somnolence. We have found this medication to be overall well tolerated and useful for treating symptom flares in patients with CP/CPPS. The starting dose is 50 mg every 4–6 h orally as needed. A usual effective dose is 200–400 mg per day with a maximum of 800 mg per day ***(50)***.

4 Medications to Treat Muscle Spasticity

A common observation of men with CP/CPPS is that of discomfort in the perineal area and feelings of spasm in the pelvic floor. Increased muscle tone in the pelvic floor has been observed in studies in men with CP/CPPS compared with controls. A comparison was performed of 62 men with CP/CPPS and 89 asymptomatic controls who underwent a standardized musculoskeletal exam ***(51)***. The men with CP/CPPS had significantly in creased levels of muscle tone, pain with internal transrectal palpation of the pelvic muscles, and increased tension and pain with palpation of the levator ani and coccygeus muscles. The pelvic pain patients also had greater pain and tension with palpation of the psoas muscles and groin. There were no differences in testing of the lower abdominal and oblique muscles. There were no differences between subtypes IIIA or IIIB CP/CPPS. Men with CP/CPPS also have abnormal EMG activity in the perineal muscles ***(52)***. In comparison with asymptomatic men, those with CP/CPPS show greater surface electromyography instability in their resting baseline tone. They also had lower voluntary contraction amplitude.

In a study by Zermann et al. ***(16)***, patients with CP/CPPS were examined and also underwent urodynamics with measurement of pressures in the area of the external urethral sphincter, the skeletal muscle component of the continence mechanism. On baseline physical examination, there was pathological tenderness of the striated muscle with poor-to-absent pelvic floor function. Average sphincter pressure was increased to 104.9 cm. water in 72.6% of the patients, average peak urine flow was decreased to 9.9 mL. per second in 61.9% and functional urethral length was increased to greater than 35 mm. in 79.8%. Looking at urethral sphincter function with voiding, the authors described the pattern as dysfunctional, obstructed, and combined dysfunctional and obstructed in 52.4, 11.9, and 21.4% of the cases, respectively, while in 88.1% urethral sensitivity was minimally or markedly increased.

4.1 Cyclobenzaprine

Cyclobenzaprine is a medication closely related to the TCAs. This drug has been used for the treatment of musculoskeletal conditions such as low back pain, whether spasm has been present or not ***(53)***. Cyclobenzaprine is a centrally acting muscle relaxant. The inhibitory effect of this medication on reflex potentials is mediated by inhibition of descending serotonergic systems through 5-HT ***(2)*** receptors in the spinal cord ***(54)***. Data from studies of cyclobenzaprine in the treatment of back pain with spasms have shown response significantly greater than that of placebo for a 5-mg and 10-oral dose three times daily for a 1-wk period ***(55)***. Onset of relief was apparent within three or four doses of the 5-mg regimen. Doses of 5 mg po three times daily are recommended for relief of muscle spasm The most limiting side effect is sedation; we have used starting doses of 10 mg per mouth qhs to minimize sedation in young working individuals during the day. Cyclobenzaprine has also been successfully used in fibromyalgia, another chronic pain syndrome with some symptoms that overlap those of C/CPPS ***(56)***.

4.2 Tizanidine

Tizanidine is a centrally acting alpha-2 agonist ***(57)*** that has been shown to be superior to placebo in treating spasticity in a number of conditions ***(53)***. The alpha2B-adrenergic receptor subtype mediates the analgesic effect of intrathecally administered Tizanidine in animal models of neuropathic pain ***(58)***. Doses starting as low as 2 mg by mouth qhs can be used and go up to three times daily. Doses of up to 36 mg orally per day have been used; we have not usually used such high doses, and the limiting side effects are somnolence and dizziness ***(59)***. Tizanidine is also used for treatment of muscle spasticity in other conditions such as spinal cord injury ***(60)*** and multiple sclerosis ***(60)***.

4.3 Montelukast

CP/CPPS and interstitial cystitis/painful bladder syndrome (IC/PBS) share many similarities, including the presence of pelvic pain and often voiding symptoms ***(61)***. The entrance criteria for the NIH sponsored Interstitial Cystitis Database and Chronic Prostatitis Cohort Study contained many similarities and allowed for the entrance of men into either study. Therefore medications that are used to treat IC/PBS may be useful in men with a diagnosis of CP/CPPS. Montelukast (Singulair) is a leukotriene antagonist that binds to the cysteinyl leukotriene receptor type 1. It is commonly used for asthma as it reduces inflammation in the lungs and has been described for the treatment of IC ***(62)***. At doses of 10 mg by mouth once daily, it has few side effects and may be effective in some men with CP/CPPS, especially those with concomitant voiding symptoms and bladder pain.

5 Surgical Therapies for CP/CPPS

5.1 Bladder Neck Incision

Incision of the bladder neck has been reported to be effective in men with prostatitis and evidence of bladder neck dyssynergy on videourodynamic studies ***(63)***. This represents a very small and specific group of patients. The diagnosis must be made using videourodynamics in which poor funneling of the bladder neck will be observed. Initial treatment in these men should be with an alpha adrenergic antagonist since the bladder neck is rich in alpha receptors ***(64)***. However, in refractory cases bladder neck incision is an option. Great caution should be used however, especially in young men since there is the risk of retrograde ejaculation which can impair fertility. Marked improvement in average IPSS symptom score from a mean of 27 preoperatively to 4 postoperatively has been reported ***(64)***.

5.2 Neuromodulation

Neuromodulation may play a role in treating CP/CPPS. The Interstim device (Medtronic, Minneapolis MN) is used in detrusor overactivity and urinary retention. It has proven effective in large groups of patients with LUTS with a response rate of 56% of patients with urgency-frequency reporting a greater than 50% reduction in voids per day at 2 yr of follow up ***(65)***. The exact mechanism by which neurostimulation improve symptoms is not completely known but it appears to work at both the level of bladder/lower urinary tract afferents in the pelvic nerves ***(66)***, as well as having activity in higher cortical centers ***(67,68)***. Interstim has been used also in patients with chronic pelvic pain. Nine of 10 patients with chronic pelvic

pain reported improvement after implantation ***(62)***. This technique has been reported to decrease narcotic use in women with IC/PBS ***(69)***. It certainly may be useful in patients with CP/CPPS who have significant urinary frequency and urgency refractory to standard oral medications.

6 Conclusion

One of the unanswered questions in CP/CPPS or any chronic pain condition is why an acute pain event becomes a chronic pain condition. As summarized recently by Ursula Wesselmann ***(70)***, what we will need to find out to treat CPPS is 1) is it possible to prevent modification of the nociceptive system and the progression from an acute to chronic pain syndrome? and 2) Can we predict which patients are at risk to develop a chronic pain syndrome after an acute pain event? Although we do not know the answer to these questions, at least we are starting to recognize that what we are treating is not an ongoing infection but a true chronic pain syndrome with neuromuscular changes that likely will respond better to the treatments outlined in this chapter than repeated courses of antibiotics.

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Chapter 10
The Role of Surgery and Minimally Invasive Prostate Therapies in Prostatitis

Jonathan Bergman and Scott I. Zeitlin

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Summary Prostatitis is a highly prevalent and debilitating disease. Minimally invasive therapies, including heat therapy and microwaves and electromagnetic therapy, hold promise but require prospective randomized controlled trials. Surgery should be reserved until all other therapies are exhausted. There is no definitive surgical treatment. Surgical interventions include seminal vasiculography and transurethral resection of the prostate.

Keywords Prostatitis; minimally invasive surgery; ejaculatory ducts.

1 Introduction

Inflammation of the prostate gland has been described since the early 19th century, and prostatitis is the most common urological diagnosis in men younger than the age of 50 ***(1–3)***. It has not previously and is not presently thought of as a surgical disease. It is considered when all other therapies have been exhausted. The roles of several surgeries and minimally invasive prostate therapies in prostatitis are at different stages of evaluation. The purpose of this chapter is to review the evidence for surgery and minimally invasive prostate therapies for chronic prostatitis.

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2 Heat Therapy

Heat therapy for treatment of chronic prostatitis can be divided into hyperthermia, with a target temperature range of 42–44 °C; thermotherapy, with a target temperature range of 45–50 °C; transurethral microwave thermotherapy (TUMT), with a target temperature range of 45–60 °C; and transurethral needle ablation (TUNA), which also has a target temperature range of 45–60 °C.

Transrectal hyperthermia has shown promise of subjective symptomatic improvement and possible improvements in fertility, although definitive data have yet to be collected. Low-powered studies have shown that transrectal hyperthermia does not affect fertility. Rigatti et al. ***(4)*** examined 14 men with prostatitis and found no differences in sperm morphology, motility, or count before and after treatment. Zinc, citrate, fructose, and free testosterone levels were likewise unchanged. Other studies have suggested subjective symptomatic improvement in approximately half of the patients treated, albeit without objective parameters or independent controls. Improved fertility was assumed by subsequent pregnancies, but without proof from semen analyses ***(5,6)***. In a placebo-controlled trial with a sham group, Shah et al. ***(7)*** reported similar symptomatic improvement, but with a 10% placebo effect. Side-effects of transrectal hyperthermia include catheter-induced hematuria (4%), epididymitis (2%), and hematospermia (2%) ***(8)***.

Transurethral heat therapy has been used in low-powered studies with varying success. Transurethral hyperthermia has demonstrated pain relief in approximately 27% of patients in a phase 1 clinical trial limited by short-term follow-up ***(9)***. TUMT has shown some promise of symptomatic improvement, although the mechanism of TUMT for treating prostatitis has yet to be elucidated. Hypotheses include accelerated resolution of the inflammatory process or alteration in the sensory nerves in the prostatic stroma ***(10,11)***. Transurethral thermotherapy via TUMT has shown greater than 50% symptomatic improvement for nonbacterial prostatitis, with 26% suffering side-effects including hematuria, urinary retention, transient incontinence, impotence or premature ejaculation, urinary tract infection, or epididymitis. Patients with noninflammatory chronic prostatitis/chronic pelvic pain syndrome (CPPS; National Institutes of Health category IIIB) demonstrated poor symptomatic improvement and universally felt the procedure was significantly painful ***(12)***. Choi et al. ***(13)*** reported a more favorable symptomatic improvement and lower side-effect profile, although this study included no placebo group and utilized no standardized symptom index. The only double-blinded analysis of TUMT, including a sham therapy group involved 20 patients (10 sham, 10 receiving TUMT) and demonstrated 70% response, measured by symptomatic movement, in the treatment group, with continued response at 1 yr ***(14)***. A recent TUMT study by Kastner et al. ***(15)*** demonstrated a 70% improvement in NIH-CPSI scores over baseline at 6 months and 63% at 12 months, with 77% of patients having 50% or greater improvement in pain symptoms. Sexual function was maintained, but the impact on fertility was unclear. These promising pilot data have yet to be reproduced in a high-powered, double-blinded, prospective, randomized study.

In examining five patients treated with balloon dilation of the prostate combined with thermal therapy, Nickel et al. ***(16)*** demonstrated no sustained symptomatic

improvement after 9 months. Moreover, significant side-effects, including worsened symptoms, hematuria, urinary retention, retrograde ejaculation, and urethral stricture were noted.

The use of TUNA has led to significant symptomatic improvement for patients with nonbacterial prostatitis at 3 months follow-up. Patients with high initial leukocyte counts had unchanged semen analysis before and after treatment ***(17)***. Although other pilot studies have suggested promising subjective response to TUNA at 8 months follow-up, double-blinded, prospective, placebo-controlled trials have yet to be performed ***(18)***.

3 Microwaves and Electromagnetic Energy in Bacterial Prostatitis

Microwaves have been shown to have heat-independent bactericidal effects on *Escherichia coli* and *Enterobacter cloacae* in vitro. Mean energy delivered was not statistically significantly different between the microwave and control groups, but a significant decrease in bacterial colony count was observed. In vivo studies have yet to be performed ***(19)***.

Electromagnetic energy, on the other hand, has not demonstrated heat-independent bactericidal properties. Bactericidal effects noted were attributable to increased heat generation by the electric generator ***(20)***.

4 Seminal Vesiculography

Ejaculatory duct obstruction is an uncommon but potentially correctable cause of chronic pelvic pain syndrome ***(21–23)***. Concomitant symptoms, in addition to chronic pain, often include hematospermia, decreased ejaculate volume and force, and premature ejaculation ***(24,25)***. Dilated seminal vesicles are a likely source of nociception, as shown in semen analyses, transrectal ultrasound findings, and magnetic resonance imaging.

Traditional surgical intervention for symptomatic ejaculatory duct obstruction involved open scrototomy, contrast vasography, and transurethral resection of the ejaculatory ducts. Unroofing of the ejaculatory ducts at the level of the verumontanum may lead to bladder neck injury with subsequent retrograde ejaculation, injury to the external sphincter with possible subsequent urinary incontinence, postoperative fibrosis, or recurrent duct occlusion ***(26)***. Obstruction beyond the prostate capsule involves extensive surgical exploration with a significant risk of rectal injury ***(27)***.

Retrograde transurethral catheterization of the ejaculatory ducts under cystoscopic guidance has been described. In patients with distorted anatomy; however, localization of the ejaculatory duct orifice is not always simple, and partial duct resection is often necessary for successful catheterization ***(28,29)***.

Computed tomography and magnetic resonance imaging allow detection of seminal vesicle dilation, even when visualization of the ejaculatory duct is not achieved ***(30)***. Transrectal ultrasound, when combined with ultrasound-guided seminal vesiculography, allows decompression of extrinsic cysts, and aspiration of fluid for analysis ***(31)***.

Lawler et al. ***(32)*** have demonstrated recent success with magnetic resonance vesiculography and transrectal ultrasonography with concomitant transrectral antegrade passage of a guidewire via the vesicle into the duct and subsequent balloon dilation of the duct. Reports have cited restoration of ejaculatory duct patency and improvement in chronic pelvic pain. Balloon dilation is especially useful in patients with partial obstruction or extraprostatic obstruction. Additionally, the ejaculatory duct flap valve mechanism is preserved, minimizing urinary reflux into the seminal vesicles. Stenosis extrinsic to the prostate gland could also be potentially treated by this approach. Duration of response remains unknown, and long-term data have yet to be collected. Successful minimally invasive treatments have rendered open scrototomy obsolete in most instances.

5 Other Surgery

According to Barnes et al there was >66% improvement from TURP for chronic bacterial prostatitis ***(33)***. This has not been these authors experience. In the 5–10 patients we have seen after TURP, only one had significant improvement (unpublished data).

According to Schaeffer et al in Clinical Evidence Concise there are no random controlled trials regarding the treatment of chronic prostatitis with TURP or radical retropubic prostatectomy. The jury is still out with regard to these interventions.

6 Conclusion

Prostatitis remains a highly prevalent and debilitating disease with significant deleterious effects on health-related quality of life. There is no definitive surgical treatment. Surgical or minimally invasive techniques, including various forms of heat therapy have demonstrated promise but still require well-controlled, prospective, randomized, double-blinded trials before their role in the treatment of prostatitis can be delineated. Restoring ejaculatory duct patency may provide relief for a small number of patients with CP/CPPS.

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Chapter 11
Physical Therapy for Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Jeannette M. Potts

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Summary NIH Category III chronic prostatitis/chronic pelvic pain syndrome is associated with neuromuscular abnormalities as manifested by pain, voiding, and sexual dysfunction. With techniques adopted from physical therapy, these abnormalities can be more readily identified and treated. Techniques such as biofeedback, myofascial trigger point release, and relaxation have been applied successfully in this group of patients. This approach, although more time consuming and low tech, affords patients with safe effective tools for self care and empowerment.

Keywords Prostatitis; pelvic pain; myofascial trigger points; biofeedback; muscle re-education; physical therapy.

1 Introduction

The term prostatitis should be applied with caution because it conjures a disease of pain arising from an inflamed or infected prostate gland. This ideation perpetuated the prostatocentric approach to the disease for decades, despite the lack of evidence for an infectious etiology or prostatic abnormality in the majority of cases. Several investigators have shown only a 5–7% yield of bacteria in specialized cultures of prostatic fluid among symptomatic men ***(1)***.

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Attempts to treat this disease as a urological condition or, specifically, an affliction of the prostate gland, have fallen short of providing adequate and consistent relief or durable responses. Indeed, treatments such as antibiotics, antiandrogens or alpha blockers, all targeting the allegedly ailing prostate gland, have resulted in responses no better than placebo. In one study, evaluating 100 men, during a series of monotherapies, only 19% of men reported significant relief of their symptoms, after 1 yr of follow up ***(2)***.

Fortunately, during the NIH National Institute of Diabetes and Digestive and Kidney Diseases consensus meeting in 1995, this most common form of prostatitis was redefined through its new classification label: National Institutes of Healh category III chronic prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) ***(3)***. This new classification system expanded the scope for this disease entity, allowing for a multidisciplinary and holistic approach to study, evaluate, and treat these patients. Physical therapy is one of such approaches that effectively identifies and treats abnormalities that cause and perpetuate symptoms typically ascribed to CP/CPPS.

2 Reframing the Symptoms

2.1 Pain

Pain or discomfort is usually described as a dull ache in the pelvic area, groin, perineum, and/or genitals. It may become intermittently intense, sharp, or severe. Some patients describe sitting on a golf ball, a foreign body sensation within the perineum or inside the rectum. Along with these symptoms, patients may paradoxically experience numbness or tingling in these same regions, and these changes may be migratory.

Review of the colorectal literature reveals similarities among patients suffering from rectal pain, who also report the sensation of “sitting on a golf ball.” Colorectal experts such as Thiele and Sinaki have noted tense pelvic floor muscles, particularly the levator ani muscles, in these patients ***(4,5)***. Treatments to strengthen and relax these muscles have been recommended. Interestingly, most of these patients were female, in whom the golf ball sensation could not be blamed upon an alleged abnormal prostate gland.

Pain previously ascribed to bladder inflammation in women suffering from interstitial cystitis is no longer being approached as a painful bladder syndrome but rather a bladder pain syndrome, which emphasizes other important elements of pelvic floor health, micturitional functioning, and neuromuscular influences (Proceedings of the IC/PBS Meeting in Bethesda, Maryland, October 2006).

In general, advances in pain medicine point toward a more holistic approach not only to treatment, but to the diagnosis of pain syndromes in our patients. We are reminded that pain perceived by our patients at specific sites may actually arise from separate sources or faulty transmission of pain signaling. Regardless of

subspecialty or body region, it is widely believed that all chronic pain sufferers should be evaluated and treated, using a biopsychosocial approach. It is clear that increased stress or anxiety contributes significantly to symptom severity. Nickel and colleagues ***(6)*** observed the strong correlation between catastrophizing and higher symptom scores as measured by the NIH Chronic Prostatitis Symptom Index (CPSI).

2.2 Voiding Dysfunction

Many patients experience concomitant lower urinary tract symptoms (LUTS) such as urinary urgency, frequency with or without burning, or dysuria. They may notice hesitancy or difficulty initiating a stream or an overall weakening of the force of stream. Still, others may be disturbed by nocturia, which disrupts sleep and further exacerbates anxiety levels in these patients. Some prostatitis patients with LUTS, studied urodynamically, demonstrate bladder outlet obstruction caused by smooth muscle tension at the bladder neck or external sphincter dyssynergia, which is defined as the nonrelaxation of the external sphincter muscle during micturition. Although some investigators have referred to these as voiding dysfunctions previously misdiagnosed as prostatitis, perhaps it may be more accurate to refer to these voiding abnormalities as components of the NIH Category III CP/CPPS ***(7)***.

LUTS are also associated with other pain syndromes such as female pelvic pain and fibromyalgia. For example, female urethral syndrome, defined as urinary frequency, dysuria, and suprapubic pain, was identified in 18% of patients diagnosed with fibromyalgia in one series. No female urethral syndrome was identified in >200 matched controls ***(8)***. Dyssynergia in children is associated with functional bowel problems, constipation, and ineffectual toileting. These disorders respond well to biofeedback ***(9)***. (This serves as a reminder to query our adult patients about their bowel functioning!)

2.3 Sexual Dysfunction

Approximately half of patients with CP/CPPS have reported ejaculatory pain ***(10)***. Men suffering from pelvic or genital pain are certainly less aroused sexually and may complain of decreased libido. Their pain may be exacerbated by arousal or ejaculation, further influencing the avoidance of sexual activity. Erectile dysfunction is reported by many men with this condition and may be episodic for some patients, as episodes may coincide with pain flare-ups. Painful ejaculation or dysorgasmia is a common complaint, but pain might also be experienced during the hours or days following ejaculation, even in the absence of dysorgasmia.

Shoskes and collaborators ***(10)*** found that patients who suffered with more persistent episodes of ejaculatory pain had more severe symptoms as demonstrated by

higher NIH-CPSI scores. These men were more likely to be younger, living alone, and to have lower income levels. Most importantly, there were no differences between those who experienced ejaculatory pain and those who did not, in terms of previous history of infection or sexually transmitted disease, positive localization cultures, or the presence of inflammation. Indeed, most men had no history of, nor evidence of previous infection.

Because patients perceive this discomfort as their response to something inflammatory or caustic in their semen, it is sometimes difficult to convince them of other possibilities such as abnormal muscular spasticity or exaggerated pelvic floor tension during orgasm. It is difficult to prove this theory as it would require electromyogram and other recordings during and after ejaculation in patients and controls. However, we have treated many men with these symptoms without the use of antibiotics, instead using pelvic floor exercises and biofeedback. In some men in whom dysorgasmia was associated with absent or low semen volumes, normal ejaculation returned after successful therapy, leading the author to wonder about some variation of retrograde ejaculation caused by yet another form of dyssynergia.

2.4 Muscles, Nerves, and the Pelvic Floor

The notion of pelvic floor myotonus or myalgia is nothing new nor unusual. Spasm of the levator, coccygeus and piriformis muscles as the cause for coccyx area pain was first described by Thiele in 1937. Of 69 patients treated by means of a transrectal massage administered on average 11 times during an 11-wk period, 60% were cured and 35% experienced "definite improvement." During the 1960s, Dr Thiele, observed an increased incidence of patients complaining of pelvic and rectal pain. He noticed that many patients had an exaggerated subluxation, or inward positioning of the coccyx and contracted or shortened levator ani muscles ***(4)***. He correlated this to repetitively poor sitting habits, which he later called the "television disease," as television became more widely available in the home at this time. I believe our contemporary variant is "computer disease."

He developed an internal digital massage technique, which incorporated the methodical sweeping and lengthening of the affected muscle, along and parallel to its orientation. This technique, known still as the Thiele massage, is performed as part of pelvic floor physical therapy for pelvic pain in men and women.

In 1977, Sinaki and colleagues published their study of 94 patients found to have "tension myalgia of the pelvic floor." In this article, these authors introduced the concept of a pelvic muscle syndrome to better define and address the myriad of diagnoses used to describe these patients: Coccygodynia, levator ani syndrome, procatalgia fugax, or rectal pain. These patients were treated with a combination of diathermy, Thiele's massage, and relaxation exercises ***(5)***. More than two-thirds of the patients were believed to have made "good recovery." The diagnosis of tension myalgia, according to Sinaki et al., is simple; however, it is "usually obscured by plethora of multiple, vague, and chronic complaints in a patient who is often neurotic."

This patient population had undergone orthopedic evaluations, radiological exams, neurological examinations, and psychiatric assessments to address stress and anxiety, all of which revealed no significant pathology. Although these were colorectal patients, we can recognize similar characteristics and lack of abnormalities among patients with CP/CPPS. My favorite part of this paper is the following passage: "The definitive diagnostic test is the rectal examination. The use of the rectal examination; however, designed to find hemorrhoids or fissures, or to palpate the prostate, may be inadequate, because the levator ani, coccygeus, and pyriformis muscles and their attachments are most often NOT carefully palpated." In other words, the standard digital rectal exam is, in my opinion, a half-assed exam. And, hopefully, after completing this chapter, the reader might be inspired to perform more thorough evaluations of his or her patients.

Segura et al. ***(11)*** proposed this broader perspective in the management of patients with prostatitis or prostatodynia in 1979. But, even before this, Dr. Janet Travell had treated President Kennedy for myofascial pain of the pelvis during his presidential campaign. She later became the White House physician ***(12)***.

Nearly half of our patients diagnosed with CP/CPPS experience voiding dysfunction, which in some instances has been proven urodynamically as a form of external urinary sphincter dyssynergia. Up to 80% of CP/CPPS patients in the series by Zermann and colleagues ***(13)*** demonstrated dyssynergic voiding. They also observed what is described as inefficiency in dynamic control of the pelvic floor (ability to voluntarily contract and relax pelvic floor muscles) in 88% of 103 patients evaluated. They hypothesized that the functional compromise of the pelvic floor musculature may induce aberrant changes within the central nervous system, which may result in a state of chronic pain.

In 1987, Meares described an "acquired voiding dysfunction" demonstrated on video-urodynamics, among men with prostatodynia ***(14)***. We can see the similarities between our patients and those historically diagnosed as Hinmann's syndrome or non-neurogenic neurogenic bladder.

It has been proposed, by Anderson and Wise ***(15)***, that genitourinary disorders, such as voiding dysfunction and ejaculatory pain, are intimately related to the autonomic nervous system and smooth/striated muscle balance. "Any number of acute or chronic stress factors working via the sympathetic endplate may be involved."

Musculoskeletal sources of chronic pelvic pain in women are well recognized. Groin and pelvic pain may originate from muscles exhibiting weakness and abnormal shortening. Causes include sleep disorders, fatigue, microtrauma (poor posture, poorly fitted clothing or shoes), macrotrauma (infection, surgical or traumatic injury), systemic disease or psychosocial stress ***(16–18)***. Specifically, pelvic floor, genital and rectal pain can be attributed to adaptive shortening, weakness, or strain of the pelvic floor muscles. Abnormalities localized to the iliopsoas, psoas, hip adductors, and the obturator muscles may manifest with similar pain distributions. Many of these findings are consistent with myofascial trigger points defined as painful nodules or taut bands identified by the examiner during careful palpation of muscles. Palpation of such points may elicit twitch responses and/or referred pain and may reproduce patient symptoms. In turn, myofascial trigger points can lead to

deconditioning of the muscle, loss of range of motion and occasionally cause autonomic dysfunction as well ***(19)***.

These observations, spanning the literature of several subspecialties (colorectal surgery, urology, and gynecology) have led many investigators to use physical therapy techniques in the evaluation of men and women suffering from genital and/or pelvic pain complaints. Further, the physical therapy methods such as biofeedback, myofascial trigger point release, and personalized exercise instruction have been successfully prescribed in the management of these patients.

In his series of 43 patients previously diagnosed with chronic prostatitis, in whom pseudo-dyssynergia was urodynamically proven, Kaplan ***(7)*** reported a >90% success of symptom relief using biofeedback. In 2004, Clemens and colleagues ***(20)*** used biofeedback and pelvic floor re-education/ bladder training for men with chronic pelvic pain syndrome. Fourteen of the 19 men enrolled in the study underwent pretreatment urodynamics. The various urodynamic findings (detrusor instability, hypersensitivity to filling, pseudo-dyssynsergia), however, did not predict treatment results. Overall, there were statistically significant improvements in all symptom parameters measured by AUA symptom score, 10-point visual analog pain and urgency scores, and voiding logs. Interestingly, only half of the patients completed the full treatment course, prescribed as six sessions.

Biofeedback was again the therapeutic modality in a series by Cornel and colleagues ***(21)*** in Holland. Thirty-one of 33 men initially recruited completed the program, which included weekly and biweekly physical therapy up to six or eight treatment sessions. These patients responded quite favorably as demonstrated by the improvement in NIH Chronic Prostatitis Symptom index (pretreatment mean, 23.6; posttreatment mean, 11.4) and pelvic floor electromyogram measurements during rest which improved from mean 4.9 mV at initial visit, to mean 1.7 mV. (Normal resting tone is considered to be <2.0 mV).

Pelvic floor myofascial trigger point release of the pelvic floor was studied for the treatment of interstitial cystitis and (urinary) urgency frequency syndrome. In this series by Weiss, 7 of the 52 patients were men. Of 42 patients with urgency-frequency syndrome, 83% of patients experienced either complete resolution or moderate to marked relief of their symptoms. Of 10 patients diagnosed with interstitial cystitis, 70% reported moderate to marked improvement ***(22)***. The author believes that pelvic floor physical therapy "arrests the neurogenic trigger leading to bladder changes, decreases central nervous system sensitivity and alleviates pain due to dysfunctional muscles."

Most recently, Anderson and colleagues ***(15)*** employed myofascial trigger point release and paradoxical relaxation (See Table 1 for definitions) for the treatment of 138 men diagnosed with CP/CPPS, refractory to "traditional" therapy. Patients received a minimum of weekly treatments for 4 wk, but some received biweekly treatments for 8 wk thereafter. Approximately half of the patients treated had clinical improvements associated with a 25% or greater decrease in all symptom scores, which included NIH-CPSI and PPSS. According to Global Response Assessment, 72% of patients reported marked or moderate improvement. The authors propose a new understanding of CP/CPPS in which certain types of pelvic pain reflect a

Table 1 Definitions of Modalities Used in Physical Therapy

Myofascial Trigger Point Release: A form of neuromuscular therapy aimed at softening connective tissues that have become taut or rigi, and restoring mobility to the muscle fascia. These hyperirritable points on the muscle or connective tissue cause local or referred pain. The treatment or "release" of these points is done ischemic compression (usually 60–90 min), deep friction, deep stripping, and lengthening/stretching.

Biofeedback: A helpful tool to help patients avoid unnecessary increased resting muscle tone. Surface EMG can be used for this purpose, as patients see and interpret the measurements and practice relaxing and "quieting" muscles.

Deep Friction: This is a type of friction in which the therapist's fingers do not move over the skin, but rather, move the skin over the tissues beneath. Examples of this technique are cross fiber and circular friction.

Skin Rolling: A simple technique to free subcutaneous fascia, or petrissage. The skin is gently picked up and pulled away from underlying structures. The skin is then released from the fingertips and adjacent skin is lifted. This is done repeatedly over afflicted body regions.

Injection Therapy: A valuable adjunct or monotherapy for trigger point release, especially when manual techniques have been unsuccessful or not feasible as in the case of severe pain. Also, it is a more immediate means of inactivating a trigger point and is helpful for patients who may not have access to further skilled manual therapy or for those with limited treatment times. Substances should be the least myotoxic, such as procaine. Combinations with epinephrine or corticosteroids have been shown to be most damaging to muscles and should be avoided.

Dry Needling: A form of injection therapy in which no substance is actually injected, but rather, the tip of the needle is introduced beneath the skin's surface to multiple loci associated with one trigger point. It is purported to be as effective as injection therapy but is associated with more soreness in the immediate postprocedure period.

Effleurage: A Western Massage technique that involves sliding or gliding over the body with continuous motion.

Paradoxical Relaxation: A form of progressive relaxation pioneered by Dr. Edmund Jacobsen nearly 100 yr ago. The paradox is that you relax, once you accept tension. Advanced techniques as outlined by Anderson and Wise, involve Respiratory Sinus Arrhythmia Breathing exercises.

"self-feeding state of tension in the pelvic floor, perpetuated by cycles of tension, anxiety and pain." Their treatment protocol offers both a safe and effective therapeutic option for the many patients experiencing pelvic pain.

3 Evaluation of Patients With CPPS

To recognize and treat this common disorder, a medical practitioner must first be aware of its existence and, second, be willing to invest his time to learn and practice this more comprehensive exam. This author also believes that these patients in particular require special engagement from their doctors, which is manifested by the thoughtful manner in which their diagnosis is formulated.

In addition to the traditional urological history and review of systems, it is important to query the patient about occupational and recreational activities. Both sedentary lifestyles and overactive/ overzealous exercise habits may be precipitating or perpetuating factors. Orthopedic injury of the back or lower extremities should be explored and assessment for any residual defect or sequelae should be addressed. A methodical evaluation of the back, abdominal wall, pelvic floor, and lower extremities is paramount in the evaluation of any patient genital and/ or pelvic pain.

Because faulty posture may contribute to abnormal lengthening or shortening of the muscles of the abdomen and pelvis, resulting in pelvic pain, we begin our evaluation by assessing the patient's posture in standing, sitting, and supine positions ***(18,23)***. Positioning of the thoracic and lumbar spine (kyphosis, lordosis, scoliosis, etc), pelvic obliquity, and resting position of hips are noted. Range of motion is tested actively and passively to assess muscular or joint restrictions ***(24)***. In patients with a history of lower back pain or a history of injury or degenerative disease, McKenzie-based mechanical evaluations are performed to differentiate lumbosacral from muscular sources of pain ***(25)***.

The examiner should bear in mind the various patterns of referred pain, characteristic of musculoskeletal sources. Pain arising, for example, from the sacroiliac joints may be perceived as discomfort in the posterior thigh, buttock, and pelvic floor (Table 2). The muscles of the abdominal wall as well the iliopsoas, are examined while the patient is positioned in a supine position. Length and symmetry of the psoas muscles can be measured indirectly by asking the patient to flex one of his legs and to allow the other to hang freely off the examination table from the level of the hip. Inability for the resting thigh to assume a horizontal or below horizontal angle is a positive Thomas test, an indication of shortening or contracture of the hip flexors ***(26)***. Patients are repositioned on their sides to assess the quadratus lumborum muscle group and the adductors.

For adequate assessment of the pelvic floor muscles, I prefer the lithotomy position for ease in performing an external examination of the genitalia and muscles, as well as internal examination via the rectum. Thoughtful palpation of the muscles is done to identify myofascial trigger points. Clues to their location may be provided by the patient's history and description of pain distributions. Palpation confirms the trigger points, which are palpable nodules or taut bands. Patients can often help by offering their feedback during the exam as to the examiner's proximity to the pain, location and character of referred pain ***(12)***.

Table 2 Patterns of Referred Pain

Source	Target
Anterior levator ani	Tip of the penis
Sacroiliac joints	Posterior thigh, buttock, pelvic floor
Iliopsoas muscle	Trunk, lower abdomen, low back, ant thigh, genitals
Piriformis muscle	Low back, buttock, pelvic floor
Pubococcygeal muscle	Pelvic floor, rectum, buttock
Int/ext obturator muscle	Pelvic floor, buttock, anterior thigh
Hip adductors	Groin, pelvis, anterior and medial thigh

Finally, I perform a prostate examination and, if necessary, obtain expressed prostatitic secretions for culture. It is often rewarding to have reproduced the patient's discomfort while palpating other regions of the pelvic floor such as the coccyx or Obturator Internus muscle, and finally allowing the patient to compare the sensation when finally the prostate is examined. This method of examination, I believe, provides yet another opportunity for patient education, which is so essential in the care of these patients.

4 Treatment of the CPPS Patient

Many texts mention "muscle reeducation" or "muscle retraining." Although this is an important part of their management, it is most important to reeducate the patient about his disease and the source of his symptoms. In this respect I see myself as a guide to empower the patient and to promote self-care, both emotionally and physically.

Postural reeducation is recommended to prevent further tissue compromise. Patients are made aware of the compensatory positioning of their back and pelvis. They are provided with strategies to increase awareness and improve posture as well as muscle tone. Muscle imbalances, which manifest as tightness and/or weakness, or by patient's inability to precisely isolate and contract specific muscle groups, are targeted for home therapy. Patients receive instruction in muscle strengthening and stretching ***(24)***.

Myofascial trigger points are identified and compressed for 20–60s by the therapist in order to "release" the trigger point and aid in the lengthening of the muscle ***(19)***. There are several options for the management of trigger points. According to Kotarinos, these include manual release techniques, manual stretching with or without cold spray, myofascial release, muscle play, therapeutic stretching, dry needling, or injections ***(27)***. Deep tissue mobilization, which includes stripping, strumming, skin rolling, and effleurage, are also incorporated in the therapy for dysfunctional muscles (see Table 1 for definitions).

Trigger point release via ischemic compression can be performed digitally or with a tool/wand. Sustained pressure should never be applied over a blood vessel or nerve or if the compression induces numbness. Proper alignment of the therapist's body, thumbs, and digits (sometimes elbow for deeper tissues such as the gluteal muscles) is paramount, not only to optimize therapy but to protect the practitioner from overuse or misuse injuries. As the trigger points resolve, appropriate exercise programs can be further developed for the involved muscles and the home program expanded ***(19,24,27)***.

Pelvic floor retraining can be achieved through biofeedback and specialized exercise techniques. Through biofeedback, many patients are able to identify abnormal muscle tension and acquire the awareness necessary for targeting these muscle groups through various relaxation techniques ***(19,28)***. Diaphragmatic breathing and hand warming facilitate muscle relaxation. Paradoxical relaxation

techniques as proposed by Anderson and Wise, are believed to be very effective in achieving profound relaxation, essential for the recovery of these patients ***(15,29)***.

5 Conclusion

Historically, patients with CP/CPPS were evaluated and treated from a prostatocentric perspective. Pharmacological and surgical therapies targeting the prostate can be unsafe, cause troublesome adverse effects, and have been minimally or inconsistently effective. These traditional therapies fail to address important components of this syndrome, namely muscle dysfunction and emotional stress. Because CP/CPPS is a complex, debilitating disorder, a more comprehensive, self-care approach should be considered when evaluating patients. The broad repertoire of techniques offered by physical therapy provides patients with a safely tailored regimen, which is both effective and empowering.

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Chapter 12
A Biopsychosocial Therapy Model for Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Dean A. Tripp

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Summary Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) has long been considered a frustrating and prevalent condition by patients and treating physicians alike. Pain is noted as the cardinal symptom in CP/CPPS and is strongly associated with a host of intra and interpersonal difficulties reported by patients in domains such as pain, disability, relations, and overall quality of life. With no tenable cure insight, symptom management for patient adjustment is strongly recommended in CP/CPPS. Extending a discussion of the biomedical treatment model into the biopsychosocial model, CP/CPPS should be qualified as a chronic pain condition recognizing the negative additive impact of psychological and environmental factors in patient outcomes. Providing an empirically based reconceptualization of CP/CPPS, a review of potential treatment targets for men suffering from CP/CPPS is suggested and a novel cognitive-behavioral symptom management program is outlined.

Keywords Pain, catastrophizing, social support, qaulity of life coping

1 Introduction

The prostatitis syndromes have been frustrating physicians and patients for most of the last century. Although generally easy to identify, prostatitis had been notoriously difficult to diagnose and categorize ***(1)***. Prevalence estimates indicate that

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prostatitis is one of the most common urological conditions and that symptoms range considerably among men of various socioeconomic status, race, and age ***(2)***. For men younger than 50 yr of age, prostatitis is the most common urologic diagnosis, and in men older than 50, the third most common ***(3)***. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) has particularly high prevalence estimates worldwide (i.e., 16% in North America, 14% in Asia and Europe) ***(4,5)*** and CP/CPPS is eight times more common than chronic bacterial prostatitis ***(6)***.

The hallmark symptom of CP/CPPS has been identified as persistent pain in the perineum, pelvic area, and/or genitalia ***(2,7)***. As in other pain conditions, CP/CPPS pain does not correspond strongly with medical findings and has no standard pathology ***(8,9)***. CP/CPPS pain is significant and reported as greater than other urological conditions such as benign prostatic hyperplasia ***(7,10,11)***. The pain experienced in CP/CPPS (i.e., perineal, abdominal, testicular, penile, and ejaculatory pain) is also described as longstanding, with little change for the better noted over time. Indeed, some patient samples have reported chronic symptoms without effective or lasting relief for an average of 87 months ***(12)***. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage ***(13)***; a definition that permits psychological factors to be assigned strong potential impact. Pain has always been a major CP/CPPS symptom, but it is now being discussed and evaluated by experts outside of the Urological profession. For example, in a recent NIH sponsored meeting on chronic pelvic pain, more than 50% of the discussion centered on the psychosocial aspects and potential management models for CP/CPPS ***(14)***.

The quality of life impact of CP/CPPS symptomatology is significant and comparable with other debilitating medical conditions such as active Crohn's disease, congestive heart failure, and severe diabetes ***(15,16)***. Experts in the field suggest that the etiology of CP/CPPS is poorly understood ***(17,18)***, biomedical treatment is described as suboptimal ***(19)***, and CP/CPPS pain chronicity is difficult to manage ***(20,21)***. The etiology and pathogenesis of prostatitis-like symptoms have yet to be determined despite the numerous efforts of basic scientists and clinical researchers ***(18,22)***. Although pain complaints are the most prominent and disabling clinical manifestation of CP/CPPS for many patients, strong psychological manifestations such as depression have also been reliably reported ***(23–25)***. When considered together this body of research calls into question the ongoing therapeutic management of CP/CPPS from a purely biomedical model.

This chapter examines CP/CPPS as a chronic pain condition using a biopsychosocial perspective to help us recognize and appreciate how psychological and environmental deficits reported by these patients are related to greater pain, disability, and ultimately a lower Quality of life. In particular, the basic tenets of the biomedical and biopsychosocial model of pain will be reviewed in the context of chronic pain and the status of efficacious treatment for CP/CPPS, followed by a review of recent CP/CPPS data that has direct implications in regard to psychological and environmental contributors to pain, disability, and overall quality of life. Finally, an empirically-based therapeutic cognitive-behavioural model of symptom management will be described.

2 An Alternative to the Biomedical Model?

In what I believe may be one of the most prophetic papers published on CP/CPPS in the past 10 yr, Egan and Krieger ***(9)*** provided an excellent review of CP/CPPS status and raised the salient point that male pelvic pain was not of interest to pain researchers. To support their assertion, they reviewed 264 studies or case reports in the journal *Pain* from 1985 to 1995, noting that less than 1% (0.08%; two publications) of the research over this 10-yr period identified perineal or genital pain in their titles and that only one case report mentioned male genital pain (0.04%) ***(26)***. Their position was straightforward enough, suggesting that CP/CPPS merited consideration as a chronic pain condition and the consequence of recognizing this syndrome as such would allow a large group of symptomatic men the hope of a different perspective. This perspective would include the consideration pain and its psychological effects in a treatment modality, inviting collaboration between chronic pain specialists and urologists. As echoed in sentiments by McNaughton-Collins ***(27)***, CP/CPPS symptoms are associated with poorer quality of life, and understanding the predictors of the prominent CP/CPPS symptoms is essential to furthering patient care.

It is not unusual to hear urologists comment on their frustration in treating patients presenting with CP/CPPS. A patient's chronic pain can stress the health care provider as well as the patient, especially as patient's report continued exasperation after treatments where their symptoms (i.e., pain) are nonresponsive. Chronic pain is an experience that leads to strong demoralization of the patient because not only must they face the ongoing stress created by pain but the ongoing difficulties that pain creates in other areas of their life (e.g., loss of work, limits on previous social activities, strained familial relations). Patients with chronic pain will often search for relief but find such pursuits evasive and frustrating. Patients with chronic pain often report helplessness, hopelessness and depression, but not all do. There is tremendous variance in the impact that chronic pain exhibits in patient adjustment, with pain and disability being associated but only modestly (e.g., ref. ***28–30***). It is this intrinsic variance or unpredictability in patients suffering from chronic pain-related symptoms that we must first understand.

Our current conceptualizations on pain and the nature of individual differences in pain perception have been shaped by centuries of theoretical writings and major shifts in both culture and science (for review see ref. ***31***). The traditional biomedical model of pain assumed that a person's report of pain was represented by roughly equivalent amount of physical pathology ***(32)***. The roots of the biomedical model can be traced back to the Grecian works or earlier but many scholars point to the writings of Rene Descartes (1596-1650) and his argument for a dualistic approach to pain as a cornerstone to the biomedical model of pain ***(31)***.

Descartes suggested that the mind was a separate entity to the body and that the mind was incapable of affecting physical matter in any significant form. For Descartes, pain was a mechanical event experienced through a "straight-through" system where skin channels sent warning signals directly to the brain, allowing

peripheral parts of the body to remove themselves from possible damage. Further, he proposed that such responses were directly related to the total or amount of damage being inflicted onto the site of the injury and ensuing pain ***(31)***.

Although the dualistic approach to pain was common in medicine well into the 19th century, pain research in the 1950s provided impetus to a growing dissatisfaction with a constricted sensory model of pain. Studies showing that individuals high in anxiety tended to also report significantly greater pain were significant in demonstrating the importance of psychological status in determining pain experience (e.g., ref. ***33***). Other pain research of this period made similar suggestions in dramatic style. For example, Beecher ***(34)*** assessed requests for pain medications from soldiers taken to hospital for follow-up treatment of their war wounds incurred at the Battle of Anzio. He compared their requests for pain medications with those of civilians who had undergone similar clinical procedures. Surveying the soldiers, Beecher found that only 25% of the wounded soldiers requested pain medications, with other soldiers denying the existence of pain or suggesting they were experiencing very little pain without the need for pain medications. Collecting similar data (pain, medication consumption) in a survey of with a civilian group undergoing similar medical procedures, he was surprised that in the civilian group, 8 of 10 patients surveyed requested pain medication. Beecher interpreted these findings in light of individual differences between the two groups, suggesting that psychological factors, such as a person's "emotional state" could significantly affect his/her pain experience and expression of their experience. He concluded with the interesting observation that the soldiers with injuries, if significant enough to create a discharge from active service, may have been experiencing strong positive emotion which may have acted to counter their pain experience and thus need for medication.

With the seminal works of Melzack and colleagues to follow in the 1960s and 1970s ***(35–37)***, pain duality was once again called into question and pain experience was contrastingly promoted as a complex perceptual and individualistic experience. Melzack and Wall's primary theory of pain regulation, the "Gate Control Theory" of Pain, attempted to explain both the clinical experience of pain and to address the shortcomings of previous pain models in regard to cognitive influences on pain experience and expression. The Gate Control Theory asserted there are physiological pathways in which their activity can either augment or reduce the subjective experience of pain. There were two major systems proposed: afferent pathways in the nervous system, where pain signals travel to the brain from the extremities, and efferent pathways, where the neurophysiological influence of emotions and cognitive activity travel down the spinal cord and modulate incoming afferent signals at the dorsal horn. In this Gate Control Theory, strong negative emotional states act to increase subjective reports of pain by facilitating sensory processing, whereas positive emotional states may act to decrease subjective reports of pain by decreasing afferent processing ***(38)***.

The basic gating of pain was not described as "all-or-nothing" but was suggested to be associated with the severity or amount of distress experienced by the individual. Therefore, individuals who are quite anxious about undergoing an aversive clinical procedure or who are quite nervous about pain in general are more likely to experience

and report greater pain than individuals that are not anxious. The theory further stipulated that pain is not entirely a sensory experience but can be considered an experience subject to great variation from person to person, influenced by an individual's subjective meaning of the situation, attention, and other cognitive schemas of the individual ***(36)***.

The Gate Control Theory has been significant in understanding pain experience and fostering research and has provided significant theoretical support for a multitude of pain treatments. For example, some advances in the treatment of pain that are theoretically rooted in the Gate Control Theory include nerve stimulation through transcutaneous devices ***(39)***, heat, ice, and acupuncture ***(40)***, as well as various psychological therapies such as progressive muscle relaxation ***(38)***. Subsequent pain models have focused on particular psychological variables referred to as cognitive appraisals of pain, with environmental influences, physical factors, or pain control perceptions also considered. Turk and colleagues described a "cognitive-biobehavioural perspective" of pain in hopes of addressing the importance of environmental factors as well as the individual cognitive factors on pain perception ***(41)***. In this model, the emphasis is placed on how an individual interprets or appraises their pain experience in light of physical sensations, emotional state and environmental support. For example, if an individual believes they have poor coping skills (i.e., an inability to self-manage a particular situation or physical sensations), or that the environment is not supportive in some manner to assisting them in managing their pain (e.g., medical staff or supportive other present or immediately available), such factors may combine and manifest different degrees of anxiety or fear among individuals. In turn, increases in anxiousness may be related to helplessness and such negative feelings are likely to exacerbate the experience of pain. As suggested in the Gate Control Theory, physiological efferent pathways may be activated by strong negative emotional states, increasing sensory processing of pain sensations which can then in turn increase a person's distress. Pain research showing the significant impact of psychosocial variables such as pain appraisals has become prominent in both experimental and clinical pain samples ***(29,42,43)***.

In a revision of the Gate Control Theory, Melzack ***(44)*** integrated his previous model with Selye's model of stress ***(45)***. Termed the Neuromatrix theory, it is proposed that individuals have a somewhat genetically determined characteristic pattern of nerve impulses that are activated by either sensory input or centrally, that is independent of peripheral activation. When injured, an individual's bodily homeostasis is altered and such deviation is considered stressful for the organism, initiating neural, hormonal, and behavioural activation to restore the baseline ***(45)***. Whether physiological or psychological in nature, stress also activates the limbic system, the primary area of emotional and cognitive processing. In situations of chronic activation, there is likely a predisposition for central nervous system to become sensitized to repeated patterns of stimulation, which may act as an underlying cycle in the development of some chronic pain states (e.g., fibromyalgia) ***(46)***. The Neuromatrix theory has been described as a diathesis-stress model wherein the physiological predispositions of the person interact with the acute stressors of a

particular person's experiences ***(47)***. In such situations, pain itself should be qualified as a stressor that can have great reduction on bodily homeostasis. Further, the presence of persistent pain can keep the body in a constant state of physiological activation. Under such a physiological load, helplessness, depression, fear, or anxiety can then act to reduce the body's homeostasis further, which may act to augment pain experience.

There are several underlying neuroanatomical pathways, neurophysiological mechanisms, and several well-known psychosocial factors involved in pain experience ***(29,48,49)***. A biopsychosocial model of pain asserts that biological aspects of chronic illness (e.g., changes in muscles, joints, or nerves generating nociceptive input) affect psychological factors (e.g., catastrophizing, fear, helplessness) and the social context of the individual (e.g., social activity, activity of daily living, interpersonal relationships) ***(50)***. Following nociceptive inputs, the perception or interpretation of this pain occurs, making individual patient characteristics central components of adaptive and/or maladaptive responses. Individual patient responses to pain are undoubtedly influenced by long-held beliefs about one's inability to manage pain. Referred to as low self-efficacy, beliefs that self-generated coping responses will not likely be beneficial to the goal of managing pain are suggested to develop over a lifetime of somatic and interpersonal experiences ***(51–53)***. Beliefs of poor ability in self-management are associated with negative pain appraisals, which in turn influence subsequent coping attempts ***(29)***.

The biomedical model of pain, focusing on etiological and pathophysiological explanations for persistent pain is criticized. Indeed, 30–50% of people seeking primary care intervention do not exhibit a diagnosable disorder ***(54)*** and up to as many as 80% of people with low back pain do not have identifiable physical pathology ***(55)***. In a similar manner, recent claims are levied against urological conditions of chronic pelvic pain. As suggested by Nickel et al. ***(56)***, it is recognized by the urological practitioners that management of patients diagnosed with CP/CPPS has been bleak, especially with their data showing that treatment strategies based on sequential application of monotherapies for patients with a long history of severe CP/CPPS may be suboptimal. Other reviews of the available literature also indicate that there were few data from properly designed and implemented clinical trials on which to justify an evidence-based approach to the treatment of CP/CPPS ***(57)***. Recent opinions suggest that the effective treatment for CP/CPPS remains elusive likely the result of its multifactorial pathogenesis ***(18)***. In summary, the biomedical model to date has not been solely successful in advancing a cure for CP/CPPS.

Persistent pain should not be viewed as just a physical or psychological phenomenon. The data suggest that the experience and perception of pain is complex and maintained by biomedical, psychosocial, and behavioral variables whose associations are likely to evolve overtime within any one person. A biopsychosocial model, viewing illness as a dynamic and reciprocal process, offers an integrated alternative incorporating physiological, psychological, and social–contextual variables that may effect and/or perpetuate pain. This model provides advantages over the biomedical model, especially when examining patient reactivity to pain by considering patient physical function, demographic, cognitive/behavioral, and

environmental domains. Despite evidence supporting the importance of psychosocial variables in chronic pain ***(29,32,50,58–61)***, such variables have been largely ignored with respect to CP/CPPS pain-related symptomatology. As suggested by Potts ***(62)***, for decades chronic infection of the prostate gland has been implicated as the cause of pelvic pain in many men, and despite only 5% of men showing positive prostate gland cultures many physicians and urologists have continued to prescribe antibiotics ***(63)***. Potts ***(62)*** also suggested that causes for prostatitis-l ike symptoms should be expanded outside of the prostate and must include associated syndromes like musculoskeletal pain, myofascial pain or other functional somatic syndromes.

3 Psychological Comorbidity in CP/CPPS

Treatment from a biopsychosocial perspective must focus on providing the individual with specific techniques that are designed to help them increase feelings of control over persistent and problematic symptoms like pain. An important implication of a biopsychosocial model in pain is a need to identify the most relevant physical, psychological and environmental aspects of the population at risk. In assisting the development of greater symptom self-management, targeted modification of sensory, cognitive, behavioral, and environmental variables are suggested. The CP/CPPS literature has outlined several psychological and environmental variables that are associated with poor patient adjustment (i.e., pain, urinary symptoms, Quality of life).

3.1 Depressive and Anxiety Symptoms

Keltikangas-Jarvinen et al. ***(64,65)*** showed that high rates of depression and anxiety in their CP/CPPS samples did not decrease considerably overtime. De la Rosette et al. ***(66)*** showed that prostatitis and control patients could be discerned by elevated levels of depression and the tendency to somatize predominantly in the patient group. Egan and Krieger ***(24)*** suggested a multitude of psychological problems accompany CP/CPPS, including anxiety, depression, and stress. For some patients, stress levels were regarded as so high that the term “stress prostatitis” was suggested. In this sample, 20% of the patients met criteria for major depression but, most notably, not one of the patients examined reported being previously diagnosed or treated for depression. Alexander and Trissel ***(10)*** surveyed patients through the Internet, reporting that 78% of their sample reported depressive symptoms and 5% reported thoughts of suicide. Berghuis et al. ***(25)*** compared CP/CPPS patients with controls showing elevated patient scores for hypochondriasis and depression and impaired sexual function: they were assessed by reduced sexual contact, problems in current sexual relationships, and inhibition in forming new sexual relationships.

Further, depression, voiding symptoms, problems with male identity, insecurity, psychological distress, and fear also have been identified as common psychological symptoms in patients with CP/CPPS ***(67)***. More recently, Ku et al. ***(68)*** reported that depression in patients with CP/CPPS was correlated significantly with both pain and urinary symptoms but that anxiety did not share these relations. Potts et al. ***(69)*** suggested that CP/CPPS patients also reported functional somatic syndromes such as irritable bowel syndrome, chronic headache, fibromyalgia, and nonspecific rheumatologic and dermatologic symptoms. They also noted that depression, anxiety, sleep disorders, and alcoholism were present in their sample as was sexual dysfunction.

In combination, the reviewed data suggested that depressive symptoms are likely a common yet undertreated psychological comorbidity in CP/CPPS. The CP/CPPS depression data are remarkable because prevalence estimates of the depression in the general population have hovered around 5–6% ***(70)***. Interestingly, clinic-based chronic pain sufferer's prevalence estimates for depression have a large range extending from 16% to 45% to 10% to 100% depending on the study examined ***(71,72)***. Depressive symptoms in chronic pain patients and CP/CPPS patients may be a reactive phenomenon of loss and despair in many patients but it also may act from a stress-diathesis model as well. In such a model, depressive symptoms may be generated due to preexisting poorly developed behavioral coping strategies (i.e., avoidance, denial) or negative catastrophic thinking about symptoms and one's ability to manage life stress. It is suggested that such predisposing negative behavior and cognition can act to increase vulnerability to depression under times of extended stress, a finding shown across several chronic medical conditions ***(71,72)***. In contrast, there are also data indicating that individuals that present with little or no predisposing depressive features are also at risk following the development of chronic pain ***(71,72)***. Thus, it is best to consider emotional experiences of patients suffering persistent pain-related symptoms on an individual basis, focusing on their particular beliefs and behaviors.

3.2 Relationship Impact of CP/CPPS

Considering the sexual nature of the symptoms manifest in CP/CPPS, it is not surprising that pain is said to interfere with interpersonal relationships. For years now, research has shown that sexuality is negatively affected by symptoms such as pain and depression. Egan and Krieger ***(24)*** postulated that CP/CPPS depression is likely associated with a lack of healthy relationships, as depression is often accompanied by isolation. Depression is probably not the only factor that explains why many men with CP/CPPS may avoid romantic/sexual relationships. Instead, the type and significance of pain symptoms may have the most impact on patients' relationships. Psychological symptoms are often comorbid with the multitude of physical and sexual symptoms associated with CP/CPPS. Some patients report diagnosable anxiety disorders or elevated general anxiety, whereas others report rumination around work

and personal health related issues. Indeed, many patients with CP/CPPS have historically reported being anxious about their relationship and their sexual problems ***(73)***. More recent data on relationships also highlights sexuality as an issue in relationships of CP/CPPS men. For example, reductions in frequency of sexual contacts have been reported in as much as 85% of men with CP/CPPS and more than 50% report periodic or total impotence in response to other symptoms like pain ***(74)***.

Despite many reports examining prostate conditions and their effects on social environments, no studies had examined the CP/CPPS patient couple in regard to sexual dysfunction. This was surprising, considering that the general pain research has shown that partners of men with sexual dysfunction and partners of men with chronic pain are impacted both sexually and psychologically ***(75–78)***. Smith et al. ***(79)*** are the first to examine men with CP/CPPS and their partners with a healthy control couple sample in terms of sexuality and adjustment. They showed that patients and partners reported lower levels of sexual functioning in some domains but were comparable with control couples on measures of satisfaction and relationship functioning. In comparison to the control males, men with CP/CPPS reported greater sexual dysfunction (i.e., less desire; more erectile problems; impaired orgasm; decreased sexual satisfaction) and greater symptoms of depression. Unexpectedly, men with CP/CPPS in this sample did not report significantly decreased sexual satisfaction or relationship functioning when compared to male controls. The spouses of men with CP/CPPS reported significantly more sexual pain upon intercourse and depressive symptoms compared to female controls. In addition, patients with CP/CPPS and their partners did not differ significantly from each other with regard to sexual functioning and satisfaction, relationship functioning, or depressive symptoms.

These results suggest that men with CP/CPPS and their spouses may experience some sexual difficulties but that CP/CPPS may not have a large negative impact on patients' intimate relationships. Running counter to the previous CP/CPPS sexuality data, the authors concluded that due to the age of the patient sample and long duration of relationships of the patient couples that these findings may not generalize to the larger population of men with CP/CPPS.

In summary, relationships are significantly impacted by CP/CPPS symptoms and it may be that the treatment of depressive symptoms could prove beneficial for patients because the treatment of such symptoms in chronic pain is associated with less pain ***(71)***. It is also suggested that the management of either depressive or sexual symptoms often results in improvements in the other ***(80)***. If nothing else, the data reviewed here indicate that clinicians of men suffering from CP/CPPS should note the potential associations between patient sexual problems, relationship durations, and depressive symptoms.

3.3 CP/CPPS Quality of Life

Reduced quality of life is associated with a variety of comorbidities in CP/CPPS ***(81)***. Quality of life broadly describes how well people function in life and their

discernment of that well-being. CP/CPPS symptoms are suggested to have a similar negative effect on quality of life as have active Crohn's disease or a recent myocardial infarct ***(82)***, and studies indicate that most men with CP/CPPS report significantly worse quality of life ***(83,84)***. In the Wenninger et al. study ***(82)***, the most severe impact of CP/CPPS seemed to be on social interaction. The primary symptom of the CP/CPPS syndrome is persistent pain, which is also the optimum criterion in differentiating patients with, C. P., controls, and those with genitourinary problems like benign prostatic hyperplasia ***(85)***. Increased pain in men diagnosed with CP/CPPS is associated with worse quality of life and greater overall symptom presentation ***(20,83)***. McNaughton-Collins et al. ***(86)*** reported that poorer mental and physical components of Quality of life where associated with worsening CP/CPPS symptom severity within the National Institutes of Health Chronic Prostatitis Cohort study. Turner et al. ***(84)***, examining men in primary-care settings for 1uality of life, reported that worse 1uality of life was associated with greater pain and urinary symptoms and that pain was more robustly associated with worse quality of life than were urinary symptoms.

Although previous reports indicate that urinary scores and pain are associated with poorer quality of life in patients with CP/CPPS in primary care and urology clinics ***(84)***, more recent CP/CPPS quality of life data have shown that pain intensity acts as the strongest predictor of quality of life, even after controlling for age, urinary scores, depressive symptoms, and partner status in adjusted regression models ***(87)***. In particular, although pain and urinary symptoms were both associated with an increased likelihood of impaired quality of life, pain contributed more than urinary symptoms. Pain severity has been identified as the most influential factor for quality of life in other studies examining pain syndromes ***(88)***.

Findings showing that pain is a key factor in CP/CPPS Quality of life may have important implications for its clinical management. Although pain is repeatedly discussed as a primary symptom of CP/CPPS and CP/CPPS is regarded as a chronic pain condition ***(84)***, no previous research has focused on how pain might affect quality of life, and what physical and psychological factors might best delineate the experience of pain. As suggested by Ku et al. ***(89)***, the urological literature suggests that an in-depth biopsychosocial analysis of quality of life determinants and other important symptoms associated with poor CP/CPPS Quality of life (i.e., pain) is warranted. There are many psychological factors involved with appreciating quality of life and pain, including social support, pain-coping strategies, cognitive appraisals of pain, and other beliefs about pain.

3.4 The Biopsychosocial CP/CPPS Data

In the first study to use a biopsychosocial framework with physical, cognitive-behavioral, and environmental predictors, CP/CPPS outcomes of pain and disability have recently been examined ***(43)***. North American men enrolled in the National Institutes of Health-funded Chronic Prostatitis Cohort Study completed surveys

examining pain and disability. Particular assessments included demographics, urinary symptoms, depression, pain, disability, catastrophizing, patients' perceived control over their pain, pain contingent rest, social support, and solicitous responses from a significant other.

The results showed that greater urinary symptoms, depression, and increased catastrophizing (i.e., a pervasive negative cognitive orientation to pain that may involve excessive rumination about pain, a magnification of the threat value of pain sensations, and feelings of low ability to manage pain: feeling helpless) predicted overall pain reported by these men. Further, when the pain reports were broken down into their affective and sensory pain components, varied results were present. For example, higher levels of affective pain (i.e., pain described in terms of emotional descriptors like sickening or fearful) were significantly associated with greater depression, but elevations in catastrophizing (i.e., helplessness subscale) were the strongest pain predictor. The helplessness reported by these men is an important clinical feature of affective pain because its impact remains significant when other variables like demographics, urinary status and other environmental predictors are included in the analyses. Completing a similar analysis for sensory type pain (i.e., pain described in terms of physical sensations like throbbing, sharp, aching), helplessness catastrophizing was again shown to be a strong predictor of pain along with elevations in urinary symptoms. In regard to CP/CP/CPPS disability, worse urinary symptoms and pain predicted greater disability, but greater pain-contingent resting (i.e., reporting the use of sedentary behaviours like sitting in a chair as a method of coping with their pain) was the strongest disability predictor. Taken together, these data suggest that a biopsychosocial intervention in regard to CP/CP/CPPS pain is warranted and that cognitive-behavioral variables such as catastrophizing are evidenced as targets for change. Indeed, catastrophizing has a robust relationship with CP/CP/CPPS pain and patient adjustment.

Recently accepted research examining CP/CPPS quality of life using a similar biopsychosocial model to that of Tripp et al. ***(43)*** examined the associations between demographic, pain, urinary, psychological, and environmental predictors in men with CP/CPPS ***(90)***. In this study, demographics, urinary symptoms, depression, current pain, pain coping, catastrophizing, pain control, social support, and solicitous responses from a partner were used as predictors of the mental and physical components of quality of life. The regression models showed that poorer physical quality of life scores were predicted by worse urinary function and increased use of pain-contingent resting as a coping strategy. Further, poorer mental quality of life scores were predicted by greater pain catastrophizing (i.e., helplessness subscale) and lower perceptions of social support from family and friends. These latest data support a biopsychosocial model for quality of life in CP/CPPS, suggesting that specific coping and environmental factors (i.e., catastrophizing, pain-contingent resting, social support) are significant in understanding CP/CPPS patient adjustment.

Catastrophizing is a particularly salient factor in the recent CP/CPPS data examining patient adjustment and has been identified as a robust detrimental factor in chronic pain patients ***(29,91)***. Catastrophizing is described as the tendency to magnify, ruminate, and feel helpless when thinking about painful sensations

(29,92). As suggested by Sullivan et al. *(29)*, catastrophizing can be interpreted as similar to Beck's cognitive theory of depression *(93)*, wherein certain patients are likely to perceive misattributed psychological or physical symptoms using habitualized information processing in ways that increase the likelihood that negative outcomes are expected as fact, not possibilities. It is important to act to reduce catastrophizing in patients experiencing pain because it is described as cognitive processing that is consistent over time and without intervention is related to increased emotional distress *(29)*.

Considered together, the CP/CPPS data for pain, relationships, and quality of life suggest that a biopsychosocial model of intervention is warranted. In particular, the cognitive-behavioral variable catastrophizing is offered as a particular target for therapeutic change based on its robust and reliable association with CP/CPPS pain, disability and quality of life. An integrative biopsychosocial model of chronic pain must incorporate the mutual associations between physical, psychological, and environmental variables and the likely changes amongst these that occur over extended periods of time. Further, a model of treatment that focuses only on one of these medical/interpersonal variables is arguably incomplete.

4 A Cognitive-Behavioral Symptom Management Program for CP/CPPS?

In this section, the basic tenets of the cognitive-behavioral approach in managing pain are described. Many of the current cognitive behavioral models applied to pain also address pain appraisals and catastrophizing in particular. A cognitive-behavioral therapeutic approach is not a replacement for ongoing biomedical efforts to ease symptoms, but should it be considered a significant partner in such treatment work. This may be especially pertinent when the patient with pain is expected to experience ongoing symptoms well into the foreseeable future. Cognitive-behavioral approaches are used to aid patients in developing new skill sets to manage their physical symptoms and the distress that may accompany the life adjustments necessitated from persistent suffering. Many pain specialists today suggest that persistent pain and its related symptoms should be conceptualized as a chronic disease like diabetes because it is anticipated that without a cure, patients will do better if they engage in self-management practices for their symptoms over time.

The cognitive-behavioral model of chronic pain has been systematically reviewed showing that it is a widely applied and efficacious treatment for pain conditions. For example, literature reviews examining outcomes of cognitive-behavioral treatment (CBT) for chronic pain show that treatments reduce patients' pain, distress, pain behavior, and is associated with improvements in activities of daily function. Treatment that has focused on decreasing negative thinking and emotional responses to pain, decreased perceptions of disability, and increased orientation toward self-management are predictive of favorable treatment outcomes *(94,95)*. The CBT model suggests that cognitive factors are essential components

to patient adjustment but also includes behaviors and patterns of observable responses made by patients. It is the interaction between thoughts and behavioral outcomes that is a point of explicit patient education and skill development. CBT models suggest that individuals are not passive in their interpretation and response to the world around them. Indeed, individuals learn to respond to stressful and positive situations through learned experiences that help shape their individualized schema (i.e., organized internal cognitive representations of personal knowledge that acts in a heuristic manner) ***(93)***. It is natural that individuals in pain may occasionally respond to stressors, not as how an observer might interpret the event(s), but to how they construct their own perception of the situation(s), which is in large part based on their internal schemata.

There are several common characteristics of CBT programs. CBT programs are usually problem oriented, extensively make use self-management skills in regard to monitoring and challenging dysfunctional and unsupported thinking, teach communication skills, make use of homework-based exercises, promote activity engagement and prepare patients to anticipate setbacks in plying these new skills ***(93,96,97)***. These therapeutic tasks are used as guides to help patients identify and modify significant problem areas they may be experiencing in adjusting to persistent symptoms, like the case of chronic pain. The CBT framework is malleable and can be used in settings of one-to-one engagement or group settings as is often found in multidisciplinary pain-management programs.

Our research center, which is sponsored by the Unites States NIH, has been developing and is currently preparing to empirically examine a novel symptom management program for CP/CPPS. This Cognitive Behavioural-Symptom Management Program (CB-SMP) is unique to CP/CPPS management because it is based on current empiric findings of CP/CPPS research and reviews ***(43,89,90)***. The use of current data to guide targeting of particular variables associated with patient adjustment makes the CB-SMP "*specific*" to the pain-related fears and cognitions of the CP/CPPS population. What also makes the CB-SMP novel is that it is being examined with trained clinical urology nurses administering the program using a patient workbook to increase quality assurance of program delivery.

The patient workbook provides patients with focused readings and session-by-session homework tasks over the course of an 8-wk schedule. All of the sessions follow an agenda that the nurse leads interactively with the patients. During an initial meeting and then again throughout the program, patients are instructed on the use of particular tool referred to as the "Reaction Record" (see Figure 1). The Reaction Record directly guides patients in identifying negative thoughts associated with pain, distress and/or negative interpersonal appraisals. The Reaction Record is also the mechanism by which patients are guided in deliberating, recording, and engaging in positive coping choices. The use of a Reaction Record is necessary because many patients suffering chronic symptoms report difficulty in acknowledging or accepting their thoughts or feelings, many of which are associated with negative emotional states. Further, many people report that they are unaware that thinking that is said to occur automatically can have such significant association to choices in behaviour and the subsequent reactions that follow. It is

Date/Time	Problem Situation:	Automatic Thoughts:	Emotion(s):	REACTION:	Adaptive Coping: Doing something Different?
	What actual event led up to this event? (e.g., attempt to do some activity, movement you are afraid of, a verbal fight… etc). What upsetting physical symptoms do you recall?	What are you saying to yourself about this problem situation? (e.g., This will never change, I can't do it, If I do that it will make me worse, these symptoms are ruining my life) What were your thoughts or picture in your mind at this time? How much did you believe each thought at that time? Rate each from ***0-100%***	What emotion(s) did you feel at that time (e.g., Sad, Angry, Anxious, Happy)? How intense did you feel each of the emotions listed? Rate each from ***0-100%***	What did you actually do following your thoughts and emotion(s)? How did you react? (e.g., resting, giving up attempt, argued, verbal confrontation, tried to ignore it, etc.)	Ask: "What is the evidence that the automatic thought is true or not true for me?" "If I keep reacting like this in the future, what benefit will I get from it?" "If I had a good friend _____ in this situation what would I tell them to do?" Challenge Thought Column and Reaction Column! Then ***Go Back*** and ***re-rate emotions*** if you were to use these new thoughts to replace old ones you had.

Fig. 1 Reaction Record: When you notice Pain or mood getting worse ask yourself, "What is going through my mind at this moment?"

most useful to have patients run through the chronology of automatic thinking and reactions to such thoughts because this is a key learning task of CBT models. It is particularly important to have the patient make connections between their automatic thoughts and negative coping responses.

It is essential to have patients test out the relationships between their thinking, the emotion associated with that thinking, their behavioral responses, and the benefit they are receiving from such efforts. Perhaps a patient is managing quite well with their identified situation (i.e., pain flare-up, distressing urinary symptoms, or fight with spouse around issues of intimacy). In such cases, the Reaction Record is a useful tool to show approval and validation of such self-management. In contrast, if an individual is reporting elevated levels of catastrophic thinking, strong negative emotional response and illness-focused coping behaviours, then the Reaction Record is used as a tool to test novel methods of self-management. The Reaction Record guides the patient through an examination of the evidence for the types of thinking they are reporting (e.g., catastrophic; "this situation will never get better") and helps them to replace such thoughts with more realistic statements ("this may be difficult now, but I know that these things have worked out before and that I have always felt better in a days time") that help avoid catastrophic appraisals. This process helps patients to examine new evidence-based ways of thinking and coping and to reevaluate these proposed changes in regard to reductions in negative emotional fallout from such interpretations.

Patients may have a difficult time reporting details of experiences that they have current troubles with. To alleviate such performance pressures during the CB-SMP program, patient's are asked to complete a weekly pain, mood, social support and disability assessment, aimed to help identify concurrent areas for discussion and intervention using the Reaction Record form. The weekly assessments are essential to tailoring the session topics to the specific areas patients endorse as problematic on the assessment scales. For example, if a patient reliably reports elevated catastrophic thinking about their suprapubic pain (e.g., "This pain will never get any better."), the patient will be guided into debating this retionalle evidence in support of such thinking and asked to examine how such thinking creates greater fear, stress, that may also culminate in coping strategy choices that are associated with greater perceived coping stratergy choices that are associated with greater disability (i.e., passive/sedentary behavioural coping).

The content of the CB-SMP sessions are clearly defined in the workbook and lead by a session agenda by the urology nurse to avoid both patient burden and confusion. The initial session is an introduction to the program requirements, the program rationale, and the value of the CBT approach. In sessions 2-3, patients are actively instructed on the use of the Reaction Record in self-identifying and modifying catastrophic cognition and understanding how such thinking is associated with greater negative affect, little supportive evidence of such thinking in their environment, and how it can lead to poor choices in behavioral coping (i.e., becoming sedentary and losing social activity that was once enjoyable). During sessions 4-6, patients identify and modify deficits in social support by practicing self-assertion communication exercises with their nurse and then later with significant others in their lives. This type of communication is essential to establishing effective problem

solving in dyads, families, and in other interpersonal contexts. The particular skills of using structured statements such as "I feel…" messages are reviewed and practiced and then assigned for use with others as appropriate. Listening skills are also introduced, so patients can learn to identify when their symptoms may be interfering or biasing the messages that others are trying to provide them with. Sessions 6-7 uses the Reaction Record tool to identify and modify illness-focused behavioral coping strategies and also to help reengage the patient in physical and social activities that they have abandoned. In the final of the eight sessions, patients are instructed in ongoing problem solving and future self-management challenges following treatment. This type of maintenance concept is an essential ingredient of many self-management programs. In summary, the CB-SMP is the first comprehensive attempt to target specific empirically supported biopsychosocial variables (i.e., catastrophizing, social support) for symptom improvement in CP/CPPS. It is suggested in the observed associations between symptoms like pain, catastrophizing, social support, and quality of life ***(87,90)*** that such treatment may also act to improve quality of life in CP/CPPS sufferers.

The goals of the CB-SMP are similar in nature to those of most CBT approaches. The four major goals of the CB-SMP are to: 1) Initiate a *sense of hope* by helping patients establish the belief that the self-management of their symptoms can shift from a state of being devastating to manageable. 2) Promote *self-efficacy* in symptoms management through the acquisition of new thinking and new wellness focused behavioural coping strategies. New strategies such as non-catastrophic thinking, positive self-coping statements and mild-moderate exercise (i.e., walking program) are suggested and evaluated by patients. The practice of new skills allows patients to stop being reactive in the face of their symptoms providing a sense of mastery. 3) Break established patterns of *schema-based automatic thinking*. In the CB-SMP the practice of self-management skills takes direct aim at breaking patterns of catastrophic thinking with the Reaction Record tool. The use of the Reaction Record allows patients to build confidence that they have the ability to evoke change in the management of their condition. 4) *Facilitate long-term adjustment* by helping patients anticipate problems with their attempts at self-management. The closing session of the CB-SMP provides explicit education and discussion about self-management into the future. Patients are encouraged to practice their new skills on a regular basis, not just in times of perceived need.

5 Conclusions

The research reviewed and suggestions proposed in this chapter are designed to help emphasize that variability in patients' responses to pain and treatment is a likely outcome. When considering that pain is a very personal experience influenced by the threat value of the situation, an individual's prior history with pain, their cognitive appraisals and behavioural coping responses (i.e., catastrophizing), the social milieu in which the pain occurs (i.e., social support) and the course of the

pain pathophysiology, a wide range of individual differences in responses to pain, disability and quality of life are predictable.

CP/CPPS is only recently being recognized as a chronic pain condition as was suggested a decade ago ***(9)*** and should be examined in light of the theory and research related to the physiology of pain and the psychological suffering that such conditions manifest. In this sense, the persistent pain found in CP/CPPS should not be viewed from a restrictive biomedical model because pain is not a purely physical phenomenon but rather a complex physical, emotional, and interpersonal fusion, where the negative outcomes are suggested to advance over time if left unchecked.

Using a biopsychosocial model to conceptualize CP/CPPS symptoms and patient adjustment, physical, and psychosocial variables should be equally targeted for therapeutic improvement because it is likely the interaction between such variables that creates distressing subjective experiences for patients ***(50)***. As reviewed here, there is an obvious association between CP/CPPS psychological and social variables that predict greater pain, disability and poor quality of life ***(43,89,90)***. It is suggested that if treatment is to proceed in CP/CPPS targeting only the biomedical aspects and ignoring the psychological and social facets, then this model is inevitably unfinished.

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Chapter 13
Pain Management in Chronic Prostatitis

Amgad Abdu, Samer Narouze, and Nagy Mekhail

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Summary Chronic prostatitis pain can be a debilitating condition and it is often represent a challenge to health care providers to diagnose and treat. It usually needs a multidisciplinary approach for effective management.

Chronic prostatitis may be associated with visceral hypersensitivity and accordingly those patients deserve a trial of tricyclic antidepressants and/or anticonvulsants. In carefully selected patients -with intractable pain that failed to respond to conservative management- nerve blocks, sympathetic ganglion block, and neuromodulation techniques may play an important role.

Keywords Pelvic pain; neuropathic pain; pudendal nerve block; hypogstric plexus; ganglion impar; neurostimulation.

1 Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a debilitating condition with an estimated minimum population prevalence of 2.8% ***(1,2)***. The clinical problem of prostatitis accounts for almost 2 million outpatient visits to the urologists per year in the United States. This number represents 8% of all visits to the urologists and 1% of those to primary care physicians ***(3)***. The direct costs of medical care are approximately $4,000 per patient per year ***(4)***. The reductions in the patient's quality of life associated with the CPPS is believed to be similar to or even greater than those associated with angina, congestive heart failure, Crohn's disease, and diabetes mellitus ***(5)***.

2 Etiology

The causes of the CPPS remain poorly understood despite years of investigations. Multiple studies of the affected patients have shown different abnormalities to be associated with the CP/CPPS, including increased levels of cytokines, immunologic dysfunction, and psychological disturbances, namely; neurosis, anxiety, depression, somatization, and hypochondriasis ***(6)***.

3 Classification

Only 5–10% of patients with symptoms of prostatitis have either acute or chronic bacterial prostatitis, both of which usually respond to antimicrobial therapy ***(7)***. Most men with prostatitis symptoms, however, present with pelvic pain without evidence of infection. This condition according to the National Institute of Health (NIH) classification system for the prostatitis syndromes is called chronic pelvic pain syndrome (NIH category III) ***(8)***. It commonly manifests as pain in the perineum, rectum, prostate, penis, testicles, and lower abdomen ***(9)***. It is sometimes associated with obstructive or irritative urinary symptoms ***(10)***.

4 Symptoms

Usually, otherwise-healthy middle-aged men (peak incidence 35–45 yr) reports months or years of perineal or penile pain, sometimes the pain involves the testicles. Suprapubic, retropubic, inguinal, and sacral pain have been reported. Urinary disturbances are often mild including frequency, urgency, incomplete emptying, and reduced urine flow. Sexual disturbances including pain during or after ejaculation have been reported ***(11)***. The NIH has developed an index (see Chapter 1) to assess the severity of the prostatitis symptoms and their impact on the patient quality of life ***(9)***.

5 Management of Pain in the Prostatitis Syndromes

Currently, effective treatment for the CPPS remains elusive. There is no current approved treatment and all therapies available now focus on alleviating the patient symptoms. After exclusion of infective etiology and absence of evidence of urinary tract infection or obstructive pathology, the therapy should be guided by the patient's preferences and monitored according to scores on the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) ***(12)***.

5.1 Nerve Blocks

Nerve blocks procedures are indicated for diagnosis and treatment of chronic pelvic pain. Patients with pelvic pain of unclear etiology (including CP/CPPS) can benefit from sympathetic blockade as a diagnostic tool to clarify the origin of pain, as the visceral pain will be temporary alleviated by the appropriate block.

5.1.1 Superior Hypogastric Plexus Block

The superior hypogastric plexus (sometimes referred as the presacral nerve) is a retroperitoneal nerve plexus located bilaterally at the level of the lower third of the fifth lumbar vertebral body and the upper third of the first sacral verteberal body at the sacral promontory. Its location is in close proximity to the bifurcation of the common iliac vessels. The plexus is formed by the confluence of the lumbar sympathetic chains and branches of the aortic plexus (contain fibers that have traversed the celiac and the inferior mesenteric plexuses). It also contains parasympathetic fibers that originate from S2–S4 ventral roots. These fibers travel as the pelvic splanchnic nerves through the inferior hypogastric plexus and join the superior hypogastric plexus. Successful blockade of the superior hypogastric plexus interferes with the pain signals arising from the pelvic viscera.

5.1.1.1 Technique

The patient assumes the prone position. Skin over the lumbosacral region is cleansed by antiseptic solution. With the fluoroscopy tube rotated laterally (almost 45°) and slightly cephalad (almost 30–30°), the lower postrolateral L5 vertebral body can be identified. After correct needle placement at the anterior margin of the lower L5 body can be confirmed by vertical spread of non-ionic contrast agent in front of the L5–S1 ventral surfaces, the local anesthetic agent can be injected after careful negative aspiration. (Figure 1) Sometimes, adequate blockade of the superior hypogastric plexus requires bilateral approach. Recently, another transdiscal approach was described. It requires single needle to pass through L5–S1 disc. This approach may be technically easier than the classical approach; however, it carries a small risk of discitis.

5.1.2 Ganglion Impar (Ganglion of Walther) Block

The ganglion impar is a midline solitary retroperitoneal structure that represents the termination of the paired paravertebral chains. It is located at the level of the sacrococcygeal junction. Although, the anatomic nerve fibers interconnection of the

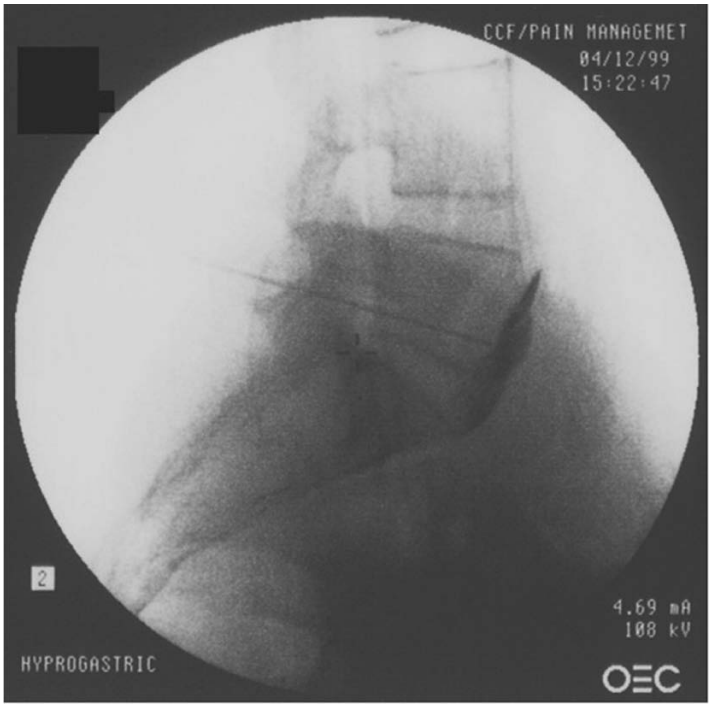

Fig. 1 Superior hypogastric block (lateral view)

ganglion is well described, it is believed that the sympathetic component of pain syndromes in the perineal region can be interrupted, at least partially, by ganglion impar blockade.

5.1.2.1 Technique

The patient assumes the prone position. Skin over the intergluteal cleft is cleansed thoroughly by antiseptic solution. Under fluoroscopy, the needle is placed in the intergluteal cleft in the midline at the sacrococcygeal junction and advanced through the sacrococcygeal ligament to be stopped less than 1 cm anterior to the anterior sacrococcygeal surface. After correct needle placement is confirmed by vertical spread of non-ionic contrast agent, the local anesthetic agent can be injected after careful negative aspiration (Figures 2-4). Neurolytic techniques such as radio frequency ablation, cryolysis, alcohol, or phenol injection are cautiously considered for sever nonmalignant refractory pain. They can be used for severe intractable pelvic pain cases with confirmed good response to local anesthetic nerve block techniques.

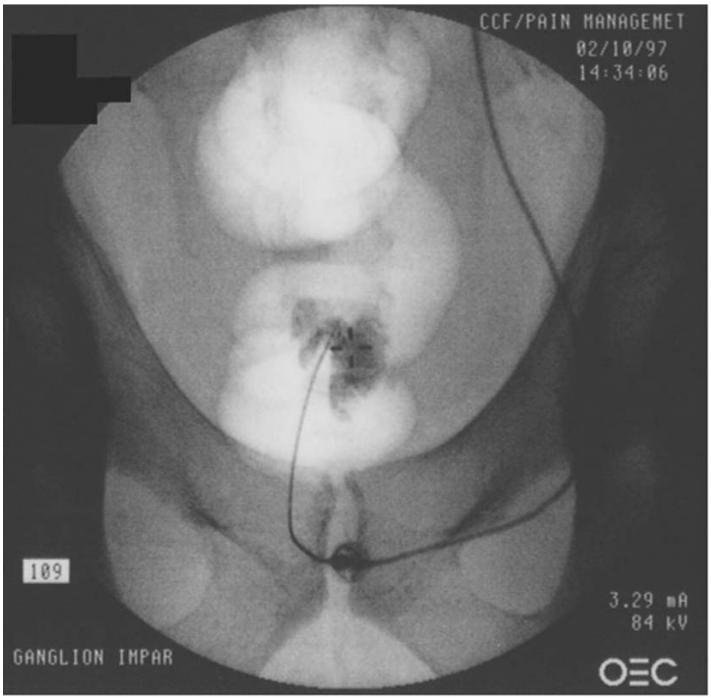

Fig. 2 Ganglion impar block (AP view)

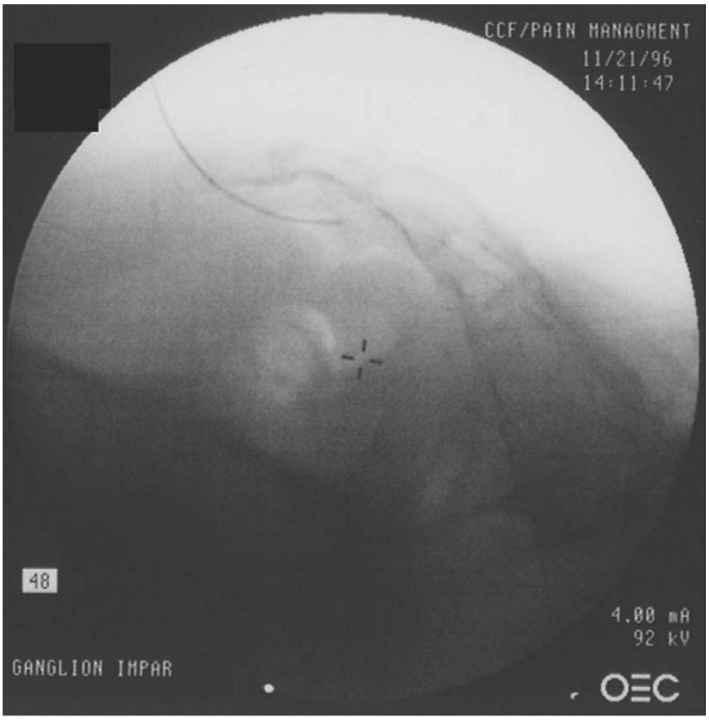

Fig. 3 Ganglion impar block (lateral view)

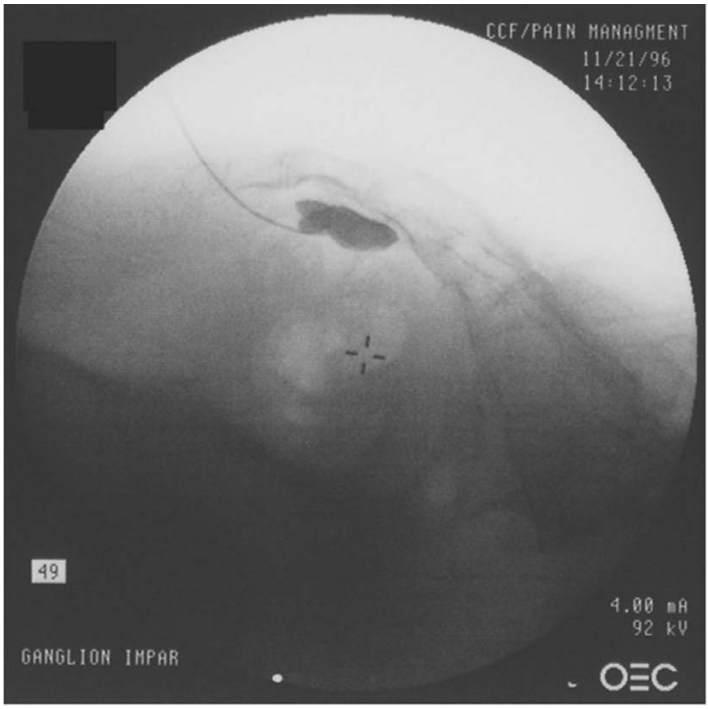

Fig. 4 Ganglion impar block (lateral view showing the contrast spread)

5.1.3 Pudendal Nerve Block

The pudendal nerve arises from the ventral primary rami of S2, S2, and S4 of the sacral plexus. It is a somatic nerve that provides motor supply to the external anal sphincter, urethral sphincter, perineal muscles, and ischiocavernosus and bulbocavernosus muscles as well as sensory supply to the perineal skin and the penis. Pudendal nerve blocks are usually indicated to clarify the type of pain arising in the area served by the nerve. Somatic pain as well as pudendal neuropathic pain should significantly improve with the block.

5.1.3.1 Technique

The patient assumes the prone position. Under fluoroscopic guidance, the ischial spine is identified and the needle is placed just medial and below the ischial spine after first contacting the bone first. The local anesthetic is then injected.

5.1.4 Neuromodulation

Neuromodultion of the sacral nerves is an effective and durable approach to multiple urological problems. The first sacral nerve stimulators implanted by Tanagho and Schmidt (1981) were performed for the indications of urinary urge incontinence, urgency-frequency, and non-obstructive urinary retention. Since that time, observations have been made for benefits beyond voiding disorders. These benefits have included re-establishment of pelvic floor muscle awareness, resolution of pelvic floor muscle tension and pain, decrease in bladder pain (interstitial cystitis), and normalization of bowel function ***(13)***. Dijkema et al. ***(14)*** concluded that electrical stimulation of S3 activates the pelvic floor and modulates innervation of the bladder, sphincter and pelvic floor, restoring the balance and coordination in sacral reflexes. (Figure 5) Nineteen of 23 patients with refractory voiding dysfunction achieved more than 50% improvement in their main symptoms after a median follow-up of 12 months. Other investigators ***(15–18)*** achieved the same results. Limited case series have demonstrated significant reduction of pain over a follow-up period of 14 to 19 months in patients with interstitial cystitis ***(19,20)***. Maher et al. reported that 73% of patients with intractable interstitial cystitis (defined as patients that have failed conventional therapy) had a reduction of pelvic pain, daytime frequency, nocturnal urgency and an increase in average voided volumes. Siegel et al. ***(20)*** evaluated 10 patients with chronic intractable pelvic pain. These

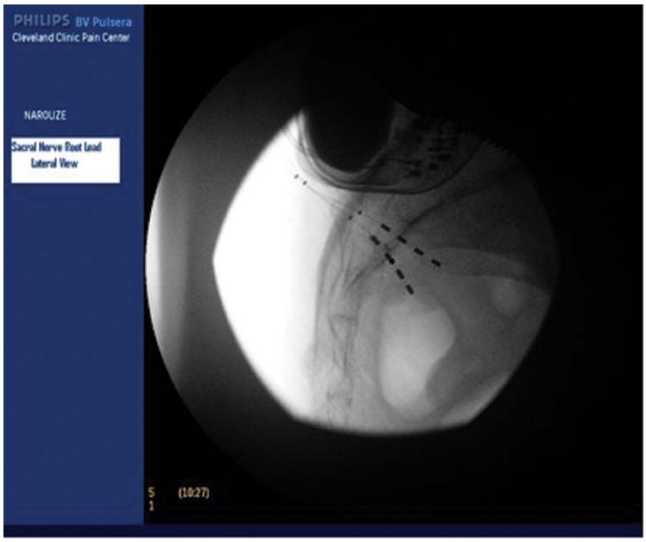

Fig. 5 Lateral view showing bilateral S3 nerve root leads

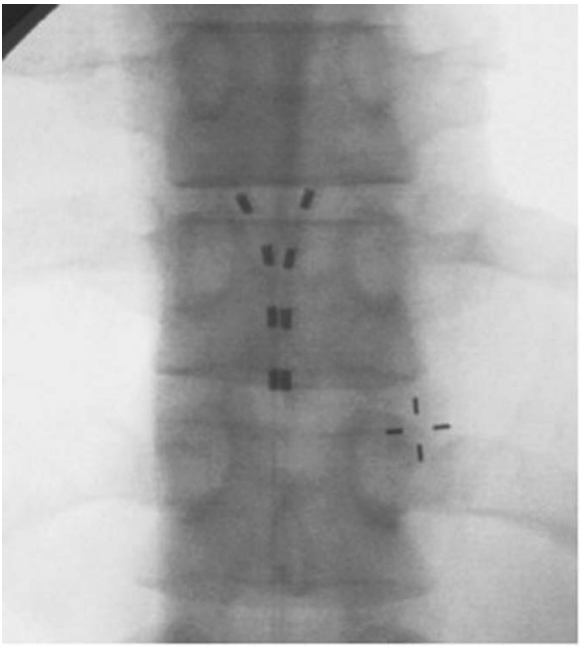

Fig. 6 Spinal cord stimulation leads at T11–12 level for visceral pelvic pain

patients, after successful percutaneous trial stimulation, had an implantable neuroprosthetic sacral nerve stimulation placed surgically. Leads were placed in the S3 and S4 in 8 and 2 cases. At a median of 19 months 6 of 10 patients reported significant improvement in pelvic pain symptomatology.

The mode of action of spinal cord stimulation is not well understood. Several mechanisms have been postulated, including the classic gate control theory; blockade of the spinothalamic tract transmission. It may function through restoring the balance between excitatory and inhibitory impulses from and to the pelvic organs at a sacral or supra-sacral level ***(22)***.

Two neurostimulation methods are currently used in clinical practice for the treatment of chronic pelvic pain: spinal cord stimulation (SCS) and selective sacral nerves stimulation. SCS is a reversible treatment for chronic pain that is gaining favor as a first-line therapy for many disease states (Figure 6). Because there are no addictive issues and no systemic side effects, the treatment is moving up the treatment continuum ladder. Technologic advances such as multi-lead and multi-electrode arrays have great impact on the clinical application of the therapy. However, several technical factors significantly limited the success of SCS in treating chronic pelvic pain syndromes. First, the cerebrospinal fluid forms a thick insulating layer at the level of the conus medullaris, which separates the dorsal column from the leads placed in the epidural space. Second, the conus is

relatively mobile in the cerebrospinal fluid inside the thecal sac, which made it difficult to maintain a consistent response when stimulating this region. Finally, stimulation has resulted in parathesia in undesirable adjacent regions of the pelvis.

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Chapter 14
Sexual Dysfunction and Infertility in Chronic Prostatitis

Lawrence S. Hakim

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Summary Chronic pelvic pain syndrome/chronic prostatitis (CPPS) is a common condition in men, accounting for a significant number of visits to primary care physicians and urologists. Sexual dysfunction, including erectile dysfunction or ED, painful ejaculation and poor libido, as well as male factor infertility, are also commonly seen in this population and are strongly associated with a negative impact on the quality of life. Although the literature strongly supports that lower urinary tract symptoms and benign prostatic hyperplasia are related to ED, there is little concrete data linking CPPS/chronic prostatitis with sexual dysfunction or male infertility. Researchers have suggested that the symptoms caused by CPPS/prostatitis, including lower urinary tract symptoms (such as urinary frequency, urgency, and dysuria) and pain or discomfort in the genitalia or suprapubic area with ejaculation, impair overall quality of life and that this is what contributes to sexual dysfunction. This chapter reviews the contemporary state of knowledge and explores the possible links between sexual dysfunction and CPPS/prostatitis, focusing on the pathophysiology and the current diagnostic and treatment options for this condition. The relationship between male infertility and CPPS/chronic prostatitis will also be explored.

Keywords Erectile dysfunction; infertility; ejaculation; chronic prostatitis; CPPS; LUTS.

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1 Introduction

Chronic pelvic pain syndrome (CPPS; including chronic prostatitis [CP]) is a common and often debilitating urologic condition. The global incidence is estimated at 10–15% of adult males and CP/CPPS is thought to effect up to half of all men during some point in their lives. There is often enormous frustration on the part of both patient and clinician, as this syndrome is often difficult to treat effectively despite the use of multiple antimicrobials and anti-inflammatory agents, and symptom relief is often only transitory.

For some patients, the onset of CP/CPPS symptoms is related to sexual activity. However, once the patient develops CP/CPPS, comorbid complaints of sexual dysfunction and painful ejaculation are often reported, which results in a significant negative impact on global quality of life. In fact, the impact on quality of life is estimated to be as great as that observed with debilitating illnesses such as Crohn's disease and diabetes. Shoskes and coworkers ***(1)*** investigated the impact of ejaculatory pain on chronic pelvic pain syndrome by evaluating men from the National Institutes of Health Chronic Prostatitis Cohort study. They demonstrated that patients with CPPS and persistent ejaculatory pain tend to have more severe symptoms, which are less likely to improve with time compared with other patients with CPPS alone. In a separate study, Tripp and associates ***(2)*** reported that depressive symptoms and pain intensity significantly predict a poorer quality of life in patients with CP/CPPS and that these effects are independent of partner status, age, and urinary status.

2 Classification and Demographics of Sexual Dysfunction

Male sexual dysfunction may be classified as erectile dysfunction (ED), disorders of ejaculation and emission, diminished libido, orgasmic dysfunction, pain disorders, and priapism. The most common of the various sexual dysfunctions are ejaculatory dysfunction and ED or impotence. ED is defined as the consistent inability to attain and maintain a penile erection sufficient to permit satisfactory sexual intercourse ***(3)***. In 1994, Feldman and associates reported on the Massachusetts Male Aging Study (MMAS), an epidemiological investigation of the medical and psychosocial correlates of erectile dysfunction ***(4)***. This large random, community-based study suggested that the prevalence of impotence from ages 40 to 70 years is more than 50%. Contemporary studies indicate, therefore, that ED afflicts more than 30 million American men and hundreds of millions worldwide.

3 Anatomy of Erection

The penis consists of two paired corpora cavernosa and a corpus spongiosum, which surrounds the urethra and forms the glans penis distally. The corpus cavernosum is surrounded by a thick fibrous sheath, the tunica albuginea, that encases the

sponge-like cavernosal tissue. The erectile tissue consists of lacunae, which are multiple, interconnected and lined by vascular endothelium. The walls of the lacunae, the trabeculae, are composed of thick bundles of smooth muscle and a fibroelastic frame, consisting of fibroblasts, collagen and elastin.

The right and left cavernosal arteries, which are terminal branches of the hypogastric arteries, supply blood to the paired corpora cavernosa, respectively. Numerous muscular helicine arteries branch off each cavernosal artery, opening directly into the lacunar spaces. Venous drainage from the corporal bodies is accomplished via multiple sub-tunical venules, located between the periphery of the erectile tissue and the tunica albuginea. The numerous subtunical venules coalesce to form the emissary veins, which pierce the tunica albuginea and drain out of the penis.

The peripheral innervation of the penis consists of sympathetic nerves arising from the eleventh thoracic to the second lumbar spinal cord segments, and parasympathetic and somatic nerves arising from the second, third and fourth sacral spinal cord segments. Somatic innervation is via the pudendal nerve, which is composed of efferent fibers innervating the striated musculature of the perineum and of afferent fibers from the penile and perineal skin.

4 Physiology of Erection

A complex series of neural and vascular interactions are necessary for healthy erectile function ***(5)***. Penile erections are initiated by local sensory stimulation of the genital organs and by central psychogenic stimuli received by or generated within the brain. A flaccid penis has a balance between blood inflow and outflow in the corpora cavernosa. Sexual stimulation triggers the release of nitric oxide (NO) into the penile tissue. Nitric oxide stimulates the production of cyclic guanosine monophosphate (cGMP). This increase in cGMP decreases cytoplasmic calcium and causes relaxation of vascular smooth muscle in the penile blood vessels and the corpora cavernosa. Relaxation of the penile vascular smooth muscle results in increased blood flow into the corpora cavernosa, which results in stretching and compression of the sub-tunical veins draining the cavernosal tissue. This increased influx of blood into the cavernosal tissue, accompanied by the decreased outflow, leads to erection. After ejaculation, activation of the sympathetic system causes an increase in tone of the smooth muscle of the helicine arteries and the trabeculae. Detumescence occurs as a result of the increased lacunar space venous outflow with decompression of subtunical venules, returning the penis to the flaccid state.

5 Causes of Sexual Dysfunction

Certain groups of patients have been found to have a particularly high prevalence of ED. In the MMAS, aging, hypertension, heart disease, hypercholesterolemia, and diabetes were among several physiologic variables found to strongly predict

impotence. In fact, ED is now considered to be a "marker" of cardiovascular disease. Although systemic vascular diseases and smoking are often risk factors for ED, certain medications, penile or perineal trauma, and radical pelvic surgery also are associated with sexual dysfunction in men ***(6)***. Various antihypertensive agents, most notably the beta-blockers, have been shown to cause ED, possibly via a decrease in corporal perfusion pressure. Digoxin, a frequently used cardiac inotropic medication, can cause ED via its effect on calcium transport in the corporal smooth muscle cell. The class of antidepressant medications known as selective serotonin-reuptake inhibitors (SSRIs) may cause decreased erectile function. In addition, the SSRI drugs can lead to an increased latency to ejaculation, making the culmination of the sexual act more difficult. An application of this "side-effect" of the SSRI family of medications is to treat the patient suffering from premature ejaculation.

Illicit drugs, including cocaine, marijuana, and alcohol, are associated with increased ED, possibly via a central neurologic effect. Cocaine is also associated with a greater incidence of priapism via its effect centrally and peripherally on calcium transport and smooth muscle relaxation. In these patients, ED may be the culmination of repeated incidents of veno-occlusive priapism, resulting in corporal fibrosis and abnormal vascular changes.

Any type of traumatic injury that effects the penile vessels, corpora, or neurologic supply can lead to abnormal corporal blood flow and diminished nerve supply. Bicycle riding and the blunt trauma, which may be associated with the constant perineal pressure from a narrow, unpadded bicycle seat or crossbar, has been implicated as the underlying cause of lower urinary tract symptoms (LUTS)/voiding dysfunction and ED in many men in this population. Sports injuries to the genitalia and scrotum are often found to be the culprit in these typically young, otherwise-healthy men.

Pelvic surgery, such as seen with patients undergoing colorectal surgery, radical retropubic prostatectomy, or cystoprostatectomy for prostate or bladder cancer, may cause ED in previously potent men. Despite a "nerve-sparing" approach, many men will experience some decrease in their potency. This loss of function is most likely a result of a combination of neurogenic and vasculogenic factors. Fortunately, there are excellent treatment alternatives available to these men to help restore them to a level of good sexual function.

6 CP/CPPS and Sexual Dysfunction

During the past 10 years, numerous investigators have shown an increased prevalence of sexual dysfunction in men with LUTS and prostatitis ***(7,8)***. A recent study by Nickel and associates looked at the prevalence and importance of painful ejaculation in sexually active men with LUTS using the International Prostate Symptom Score (IPSS) questionnaire, the bother score (IPSS question 8), and the Danish Prostate Symptom Score sexual-function questionnaire (DAN-PSSsex), which assesses rigidity of erection, amount of ejaculate and pain/discomfort on ejaculation, and

their bothersomeness ***(9)***. Almost 20% of the men studied reported having prostatitis-like symptoms of pain and discomfort on ejaculation, and there was a greater incidence of ED and reduced ejaculation associated with more severe LUTS. By contrast, in the men with no ejaculatory discomfort, fewer reported ED or reduced ejaculation.

The relationship between LUTS and sexual problems in men older than 50 was studied by Rosen and associates ***(10)***. They used a large-scale, multinational survey (the multinational survey of the aging male or MSAM-7) and several validated symptom scales, including the International Prostate Symptom Score, the Danish Prostatic Symptom Score, and the International Index of Erectile Function (IIEF). Their research showed that sexual disorders and their bothersomeness were strongly related to both age and severity of LUTS, including those found in CPPS, independent of comorbidities such as diabetes, hypertension, cardiac disease, and hypercholesterolemia.

Vallencien and coworkers ***(11)*** studied the relationship between sexual dysfunction in men with lower urinary tract symptoms, using the DAN-PSS sex questionnaire. Their study confirmed the findings in other reports, that painful ejaculation, ED, and reduced ejaculation are highly prevalent in men with lower urinary tract symptoms and are strongly related to the severity of LUTS.

7 CPPS and Premature Ejaculation

CP has been suggested as an important organic cause of premature ejaculation, a common male sexual dysfunction that affects 30–40% of sexually active men in an age-dependent manner. Shamloul and associates compared sequential microbiologic specimens in men reporting premature ejaculation with healthy age-matched men and demonstrated a high prevalence of CP in patients with premature ejaculation ***(12)***. They suggested that examination of the prostate, physically and microbiologically, should be considered during assessment of patients with premature ejaculation. Similarly, Screponi and coworkers investigated the prevalence of chronic prostatitis in men with premature ejaculation ***(13)***. They found a statistically significant increase in the incidence of prostatic inflammation and chronic bacterial prostatitis in men with premature ejaculation, as compared with the controls. Their study suggested a role for chronic prostate inflammation in the pathogenesis of premature ejaculation and stressed the importance of a careful examination of the prostate before instituting any pharmacologic or psychosexual therapy for premature ejaculation.

8 Diagnostic Evaluation of ED

The initial evaluation for ED begins with a detailed sexual, psychosocial, and medical history; a complete physical examination; and specific laboratory tests to help identify possible comorbidities. Whenever possible, the patient and partner should

be evaluated together; this may reveal underlying relationship and adjustment issues, as well as difficulties in communication.

The sexual history should focus on the degree of ED, its frequency, and the duration of the problem. Questionnaires are useful to diagnose the presence and assess the severity of ED. These include the IIEF and an abridged version of the IIEF known as the Sexual Health Inventory for Men (SHIM). Longstanding ED may involve performance anxiety and require psychological therapy as well as medical treatment.

Medical history should evaluate common risk factors for ED, as well as concomitant medications. Any history of emotional/psychological problems or of previous surgical procedures, should also be noted. In addition to the usual physical examination parameters, any anatomical abnormalities should be assessed, as well as sensory adequacy of the nerves serving the penis. The results of the initial evaluation may be further corroborated by a variety of diagnostic examinations such as neurologic, psychological, hormonal, and vascular assessment such as penile Doppler exam to assess blood flow to the corpus cavernosum. The diagnostic algorithm is illustrated below in Table 1.

With more sophisticated diagnostic evaluations, a primary organic cause of ED is often found. However, it is important to remember that either a primary or secondary psychogenic problem may contribute to the sexual dysfunction. To maximize patient success, both the psychogenic and organic factors should be addressed. In addition, sexual dysfunction is a "couple's disease." Although physicians often deal exclusively with the "patient," to improve sexual function, the partner is a vital

Table 1 ED: Diagnostic Algorithm

Patient history:
Medical and surgical history, including cardiovascular disease, diabetes, hypertension, LUTS, Medications, tobacco/alcohol/recreational drug use
Sexual and psychosocial history, level of libido
Rule out: Ejaculatory or orgasmic dysfunction
CPPS/Chronic Prostatitis
Physical Examination:
Complete exam
Abnormal penile curvature
Palpable corporal fibrosis
Digital rectal examination
Endocrinologic and laboratory evaluation:
Routine hematologic/chemistry profile, fasting blood glucose, HgA1C
Lipid/cholesterol profile
Hormonal profile (testosterone, leutinizing hormone, follicle-stimulating hormone)
Urinalysis, Urine culture, analysis of ejaculatory fluid, expressed prostatic secretions
Prostate-specific antigen
Specialized testing:
Vascular (penile duplex Doppler ultrasonography, DICC, arteriography)
Neurologic (biothesiometry, nocturnal penile tumescence testing, dorsal nerve somatosensory evoked potential and sacral latency testing)

part of the equation. ***(14)***. Efforts to include the partner in all aspects of the diagnostic evaluation and treatment decision process are extremely paramount to obtaining a successful outcome.

9 Therapeutic Management of Sexual Dysfunction

A variety of therapeutic alternatives are used for the man with ED, with or without the presence of CP/CPPS. Improving overall quality of life is a critical factor in the management of sexual dysfunction. An unhealthy lifestyle may contribute to the development of ED and chronic diseases; therefore, clinicians should counsel their patients about a healthy lifestyle. Specific lifestyle modifications should be encouraged, including smoking cessation, limitation of alcohol, eating a healthy diet, and proper exercise. New agents for smoking cessation (Chantix, Pfizer, NY) have been recently approved by the Food and Drug Administration and were shown to be safe and effective and can be used concomitantly with available ED therapies.

To maximize efficacy of sexual dysfunction treatment and improve quality of life, it is important to first treat the CPPS symptoms if possible, especially as they relate to pain and discomfort, as these symptoms will certainly exacerbate sexual dysfunction and diminish the efficacy of any ED therapy. Painful ejaculation is one of the most prevalent, differentiating and bothersome symptoms in men with chronic prostatitis/chronic pelvic pain syndrome and LUTS. Although studies have demonstrated improvement in voiding symptoms using alpha-blockers in patients with LUTS, there are a paucity of data in the CPPS literature looking specifically at the impact of these agents on sexual dysfunction. Nickel and associates evaluated the effect of the selective alpha(1)-blocker alfuzosin in men with LUTS and painful ejaculation, and compared it with those with LUTS only ***(15)***. They found that with alfuzosin treatment, men with painful ejaculation compared with LUTS alone not only had similar improvements in LUTS, quality of life, and ejaculate volume but demonstrated a significant decrease in painful ejaculation and even greater improvements in ED.

A recent study at Stanford University by Anderson and associates evaluated sexual dysfunction in men with refractory chronic pelvic pain syndrome and assessed the effects of pelvic muscle trigger point release with concomitant paradoxical relaxation training ***(16)***. The Pelvic Pain Symptom Survey and NIH-Chronic Prostatitis Symptom Index were used to document the severity/frequency of pain, urinary and sexual symptoms, with an average 5-month follow-up. Their data revealed that application of the trigger point release/paradoxical relaxation training protocol was associated with significant improvement in pelvic pain, urinary symptoms, libido, ejaculatory pain, and erectile and ejaculatory dysfunction.

When considering the treatment of ED, one can separate the therapeutic options into first-, second-, and third-line treatments. First-line treatment options for ED are simple, noninvasive, and include oral medications (such as sildenafil), psychological or sexual therapy, and vacuum constriction devices (primarily for patients who are

not candidates for oral therapy). Second-line treatments include intraurethral placement of prostaglandin E1 (i.e., MUSE), injection therapy, and combination therapy. Penile prosthesis and vascular surgery are considered third-line options and typically are reserved for patients who are unsatisfied with simpler therapies. This therapeutic algorithm is illustrated in Table 2.

Oral therapies should be considered first-line therapies for most patients with, E. D. Currently, there are three phosphodiesterase type 5 (PDE5) inhibitors available indicated for the treatment of E. D.: tadalafil (Cialis, Lilly), vardenafil (Levitra, Bayer-GSK), and sildenafil (Viagra, Pfizer). All of these oral agents are selective inhibitors of cGMP–specific phosphodiesterase type 5 (PDE5). Increased penile blood flow during penile erection is mediated by the release of NO from nerve terminals and endothelial cells, which stimulates the formation of cGMP in vascular smooth muscle cells ***(17)***. Cyclic-GMP causes vascular smooth muscle relaxation and increased blood flow into the corpus cavernosum. PDE5 inhibitors block the degradation of cGMP by competitive inhibition of the PDE5 isoenzyme, facilitating the relaxation of penile vascular smooth muscle. This facilitates the erectile process in a patient with, E. D. Because sexual stimulation is required to initiate the local release of NO, the inhibition of PDE5 by these agents has no effect with regards to erection in the absence of sexual stimulation. Possible side effects of this form of therapy include headache, flushing, nasal congestion, dyspepsia, and infrequent back pain. For any PDE5 inhibitor, administration to patients who are using any form of organic nitrates, either regularly and/or intermittently, is contraindicated due to the potentiation of the hypotensive effect of nitrates.

Hormone-replacement therapy with testosterone is used to maintain normal serum levels of testosterone and to help restore potency, energy levels, and libido. This therapy should only be used in the treatment of ED in the presence of concomitant hypogonadism. This is also important for patients receiving PDE5I therapy, as their efficacy may certainly be diminished in cases of low androgen levels. Because of the relatively unpredictable serum levels and hepatotoxicity observed with oral testosterone preparations, parenteral administration is preferred. Testosterone enanthate administered intramuscularly in doses of 200 to 300 mg can

Table 2 ED: Therapeutic Algorithm

First-line treatment options: (Simple, non-invasive)
Oral medications (PDE5-Inhibitors)
Hormonal Therapy (Androgel, Testim, IM therapy)
Psychological or sexual therapy
Vacuum constriction devices
Second-line treatments options: (Minimally invasive)
Intracavernosal Injection Therapy (Caverject)
Intraurethral placement of prostaglandin E1 (MUSE)
Combination therapy
Third-line treatments options:
Implantation of penile prosthesis
Microvascular surgery

be used every 2 to 3 wk. The amount and frequency of administration will vary with the individual and can be titrated. A newer form of hormone-replacement therapy today incorporates the daily topical application of 1% testosterone (Androgel or Testim). The major advantages of this mode of delivery include the ability to easily maintain normal physiologic levels of testosterone without injection, with no hepatic side effects. Before beginning testosterone replacement therapy in any man over the age of fifty (>40 with a family history of prostate cancer), serum prostate-specific antigen levels, a digital rectal examination, and possibly transrectal ultrasound and biopsy studies should be performed. In patients with ED and hyperprolactinemia treatments include 1) cessation of medication causing hyperprolactinemia (e.g. estrogens, alpha methyldopa), 2) administration of bromocryptine, or 3) surgical ablation or extirpation of a pituitary prolactin secreting tumor.

Vacuum erection devices are a noninvasive first-line treatment option for men with ED. These devices have three common components: a vacuum cylinder, a vacuum pump that creates negative pressure within the chamber, and a constrictor or tension band that is applied to the base of the penis after the erection is achieved. The patient places his penis within a preformed suitably sized chamber that is attached to a pump mechanism. When the vacuum pump is activated, negative pressure is created within the chamber, thereby drawing blood into the penis to produce an erection-like state. At the point of achieving adequate tumescence and rigidity, a constrictor band at the base of the chamber is transferred to the base of the penis thereby "trapping" blood within the penis. The erection resulting from the vacuum device differs from the physiologically induced erection, which is achieved by the initial relaxation of the corporal smooth musculature, allowing for engorgement of blood into the lacunar spaces. In the vacuum-induced erection, corporal smooth muscle relaxation does not occur initially, and blood is simply trapped in both the intra- and extracorporeal compartments of the penis, resulting in penile "engorgement" with a hinge-like effect. Potential complications associated with use of a vacuum erection device may include difficulty with ejaculation, penile pain, ecchymoses, hematomas, and petechiae (especially if the device is used for >30 min). Patients taking aspirin or coumadin are more likely to develop vascular complications. Finally, only physician-prescribed, pressure-regulated vacuum erection devices should be used in the treatment of erectile dysfunction. Severe morbidities, including the development of Peyronie's disease and worsening of ED, are more likely to occur with the use of commercial, nonprescription, magazine-ad type devices, which lack the pop-off pressure mechanism that is incorporated in the prescription devices ***(18)***.

For men with ED in whom simple, first-line, oral therapies are unsuccessful or contraindicated, intracavernosal pharmacotherapy can be offered as an effective treatment alternative. These self-administered intracavernosal injections of vasoactive agents serve either to directly relax the corporal smooth musculature or block adrenergic tone of the corporal smooth muscle. Various intracavernosal agents include papaverine hydrochloride, phenoxybenzamine, phentolamine mesylate and the prostanoid prostaglandin El. The mechanism of action of papaverine hydrochloride and prostaglandin El is via direct smooth muscle relaxation. Therefore, when

injected intracavernosally, they maximize arterial inflow as well as corporal veno-occlusion via relaxation of both arterial and trabecular smooth musculature, respectively. Phentolamine, on the other hand, blocks adrenergically induced muscle tone and therefore does not, alone, initiate erections, but is effective in prolonging the erectile response. A variety of solutions containing the aforementioned agents are presently being used in clinical practice: papaverine alone, papaverine and phentolamine, prostaglandin El alone (Caverject®), phentolamine, and prostaglandin El or a mixture of all three (Trimix).

The therapeutic goal of self-injection therapy is to be able to create a rigid-enough erection satisfactory for vaginal penetration that lasts between 30 min and 1 h. The initial objective of the dosage determination phase is to define the lowest dose required for achieving an appropriate erectile response. Patients are injected at first with low doses, which are then increased incrementally. After an appropriate dose has been determined, the patient is instructed in proper injection techniques. Patients are also taught to compress the site of injection for 3 min after therapy. Patients are told not to inject more frequently than three times per week. Patients who enter a pharmacologic erection program should be aware of the potential complications of this treatment, including hematomas, burning pain after injection, urethral damage, cavernositis or local infections, nodules and fibrotic changes of the corpora cavernosa, penile curvature, and prolonged erections or priapism. Patients must be cautioned to call their physician if an erection persists for 4 h or longer (priapism). Although the majority of these prolonged erections will detumesce on their own, some will require intracavernosal injection of an alpha-agonist (such as phenylephrine), corporal aspiration or surgery to produce detumescence ***(19)***.

Implantation of a penile prosthesis, also known as a penile implant or internal penile pump, can be recommended as an effective treatment option that will "fix" the problem in men with ED that are dissatisfied with their response to medical therapies or external devices, such as a vacuum erection pump or constricting band ***(20)***. A penile prosthesis allows men to achieve a rigid, often "natural feeling" and long-lasting erection spontaneously, any time, any place. Various types of penile implants are currently available for use, including malleable or semi-rigid implants and state-of-the-art inflatable penile implants and many health insurances often cover the expenses associated with the procedure. To assure optimal patient and partner satisfaction, the counseling process, including documentation of informed consent, are critical steps.

The malleable devices have the advantage of a relatively low postoperative complication rate, low cost, and ease of implantation. Component failure and reoperation rates are kept to a minimum. However, with these devices, length and girth of the penis do not change and thus may be less aesthetically desirable. Conversely, multicomponent inflatable devices are based on hydraulic principles that enable the patient to increase penile girth, rigidity and even length by inflating the device, thus simulating natural tumescence ***(21)***. The detumescence phase is also more natural and complete, providing for an improved aesthetic result. Subsequent improvements in inflatable devices have markedly reduced the likelihood of infection, reoperation and component failure.

With regard to patient counseling and device selection, it is important for the patient and his partner to recognize that no single device is best for everyone ***(22)***. There are a number of factors that need to be considered, including patient dexterity, prior surgical history, physician experience, and cost, to name a few. If a patient desires the simplest device with the lowest possible risk of mechanical failure and is willing to accept the inherent limitations, such as constant rigidity and unchanged girth, then the consideration of a nonhydraulic or malleable-type of device is very reasonable. For those men who wish to have a more "natural" erection, with improved girth and improved concealability in the flaccid or uninflated position, without sacrificing spontaneity, an inflatable implant is often selected ***(23)***. Two companies in the United States, American Medical Systems and the Coloplast Corporation, both located in Minnesota, currently manufacture inflatable penile implants. This outpatient procedure is performed through a tiny opening in the scrotum or sac, under spinal or general anesthesia and takes only 30–40 min on average for the complete procedure.

Patients need to be counseled that, as in any elective surgical procedure, there is an ever-present risk of infection with prosthetic surgery. Studies have demonstrated that the risk of penile implant infection is <1–2% in virgin implants, although it is increased in salvage and re-do surgery ***(24)***. This extremely low infection risk is due to specialized surgical techniques and, in part, to the new device coatings specifically formulated to minimize the risk of infection ***(25,26)***.

Although patient satisfaction rates after penile implant surgery remain among the highest of all therapies, the importance of proper patient selection and detailed preoperative counseling is of paramount importance. By letting patients and their partners know what they can expect during the preoperative and postoperative periods, by discussing the potential adverse events and expected changes, by allowing adequate time to address any patient or partner concerns and by assuring a detailed and documented informed consent, we can maximize patient and partner satisfaction while helping to restore their sexual function and intimacy.

In very selected patients, microvascular arterial reconstructive surgery can be offered for the treatment of arteriogenic ED ***(27)***. The goal of this therapy is to increase blood flow to the penis during erection by bypassing the site of arterial obstruction. Proper patient selection for these procedures is most critical and impacts strongly on the results of this surgery. The best candidates appear to be younger men with discrete lesions in the pudendal artery, the common penile artery or both due to pelvic or perineal trauma.

10 Infertility and CP/CPPS

There is considerable confusion about the effects of CP/CPPS on male reproductive physiology. Krieger and associates ***(28)*** evaluated seminal fluid and expressed prostatic secretions from men with symptoms of prostatitis. Seminal fluid findings were compared in men with inflammation in their expressed prostatic secretions, i.e.,

nonbacterial prostatitis, and men without inflammation in prostatic secretions, i.e., prostatodynia. They found that nonbacterial prostatitis, but not seminal inflammation, was associated with reduced sperm motility. In a related study, Ludwig and colleagues ***(29)*** investigated the impact of urogenital inflammation on standard ejaculate parameters, including pH, volume, total sperm count, sperm density, motility, morphology, vitality, and counting of peroxidase positive leukocytes. Their findings suggested that elevated leukocyte counts in prostatic secretions and in ejaculate, as indicators of inflammation, have no negative impact on total sperm count, sperm density, motility, morphology, and sperm vitality in patients with CP/CPPS.

Li and associates investigated the prevalence of CP in male infertility patients and its effects on male infertility in two studies ***(30,31)***. More than 500 male patients with complaints of male infertility were interviewed for a history of prostatic disease and underwent digital rectal examination of prostate, analysis of semen and expressed prostatic secretions. They reported that more than 39% of the patients with male infertility were diagnosed as also having chronic prostatitis. Although liquefaction dysfunction was more prevalent in male infertility patients with CP, it had little influence on the quality of semen and sperm motility.

Evdokimov and coworkers ***(32)*** reported reduced spermatogenesis and an increased prevalence of infertility in patients with chronic prostatitis. Henkel and associates ***(33)*** studied the effect of CP/CPPS on the acrosome reaction in human spermatozoa and demonstrated a significant influence of the inflammation on acrosomal functionality, which could be mediated by inflammatory mediators like reactive oxygen species. Engeler and associates ***(34)*** analyzed fertility data in men with chronic pelvic pain without evidence of inflammation in prostate secretions or ejaculate (NIH IIIB). (34) They concluded that patients with prostatitis NIH IIIB have changes in their ejaculate with a reduction of motility and a reduced fructose concentration, which they felt supported a somatic etiology of the chronic pelvic pain syndrome.

Everaert and associates ***(35)*** reviewed the relationship between male infertility and chronic prostatitis. They stressed that although the relationship between prostatitis and infertility remains unclear, bacteria, viruses, leucocytes, reactive oxygen species, cytokines, obstruction, and immunological abnormalities must be seen as cofactors in the development of infertility in patients with prostatitis.

Regarding specific treatment for men with infertility and chronic prostatitis, Deng and coworkers ***(36)*** evaluated the efficacy of biological zinc in the treatment of male infertility with CP. They reported that seminal zinc concentrations, semen liquefaction, and sperm motility were all markedly increased in the patients who were given biological zinc supplementation, as compared with those who had not received zinc. The authors suggested zinc as an effective method for the treatment of these patients, although further placebo controlled studies need to be performed.

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Chapter 15
Interstitial Cystitis in Men: Diagnosis, Treatment, and Similarities to Chronic Prostatitis

Jonathan D. Kaye and Robert M. Moldwin

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Keywords Interstitial cystitis, Hunner's Ulcer, chronic prostatitis, chronic pelvic pain syndrome

1 Introduction

Interstitial cystitis (IC) in the male patient is likely an underdiagnosed condition, given its striking clinical similarities to prostatitis/chronic pelvic pain syndrome (CP/CPPS). This chapter will explore the epidemiology, clinical manifestations, pathology, and treatments for IC with an emphasis upon the male patient. Overlapping clinical pathophysiology between IC and CP, as well as its possible effects upon patient management, will also be discussed.

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2 Definitions and Demographics

Largely a diagnosis of exclusion, IC is a clinical syndrome defined by chronic urinary urgency, frequency, and pelvic pain or discomfort in the absence of any other identifiable cause ***(1)***. The pelvic pain encountered is commonly associated with bladder filling and may lead to debilitating, although volitional, daytime and nighttime voiding. Seventy-five percent of men with IC also complain of hesitancy as at least one of their symptoms ***(2)***.

Although IC can present at any age, it is most commonly diagnosed in the third through sixth decades. Depending upon the criteria for diagnosis, estimates of its prevalence range from 10 to 55 cases per 100, 000. Men are thought to account for as few as 10% of these cases and as many as 30% ***(3)***. The true prevalence of IC in men may be significantly greater than 1–5 per 100, 000 men when taking into consideration the general underdiagnosis of IC coupled with its clinical similarities to CP ***(4)***. In fact, Clemens and colleagues ***(5)*** found that the prevalence of IC *symptoms* was actually 60- to 100-fold greater than the prevalence of a coded *physician diagnosis* of IC in the same managed care population. Additional difficulties with the establishment of accurate epidemiology for the male IC patient is that symptoms may significantly change over time, with IC-predominant symptoms gradually giving way to CP-predominant symptoms, or visa versa ***(6)***.

The "classic" form of IC is marked by gross erythematous changes of the bladder wall and was first identified by Guy Hunner in 1915. These "Hunner's ulcers" or "Hunner patches" represent panmural inflammation, fibrosis and granulation tissue. When present, they are often amenable to unique treatment modalities (see Section 7). In our series of 86 Hunner's ulcers patients, we found a 3:1 female:male predominance, a gender ratio somewhat less disparate than that observed in the significantly more common, nonulcerated IC ("non-classic" variant) population. No gender differences were noted when considering episodes of gross hematuria, presence of irritable bowel syndrome, visual analog pain score upon presentation, the number and location of Hunner's ulcers, or the presence of microscopic hematuria and pyuria ***(7)***.

An extensive description of CP/CPPS is not necessary here, as other chapters of this volume address this subject in considerable depth. For the purposes of further discussion, CP will refer to Category III patients those male patient who present with chronic genitourinary pain with or without evidence of prostatic inflammation (Categories IIIA and B, respectively) in the absence traditional uropathogens localized to the prostate gland.

3 Quality of Life

The high prevalence of IC and CP take societal tolls. Ratner and colleagues found that 50% of IC patients report an inability to work full-time ***(8)***. Of equal importance is the detrimental effects that these conditions have upon individual lives: quality-of-life

evaluations for patients with IC demonstrate scores lower than individuals receiving hemodialysis ***(9)***. Similar evaluation of prostatitis patients has demonstrated a quality of life comparable with those suffering from severe congestive heart failure, diabetes, recent myocardial infarction, unstable angina, hemodialysis-dependant end-stage renal disease, or active Crohn's disease ***(10–12)***. The decrement in these patients' quality of life most assuredly emanates in part from the physician's frequent inability offer practical treatments for this debilitating problem, or even any realistic expectation for a return to normalcy. The chronicity of often disabling symptoms coupled with delayed care, misdiagnoses, and suboptimal clinical responses worsen matters for patients. To wit, Hanash and Poole's classic study evinces the difficulty in diagnosis that IC patients have historically experienced: of their 123 male patients, 55% had undergone at least one TURP before ultimately receiving a diagnosis of IC ***(13)***. In a more recent study, Dejuana and Everett found a similar pattern: of 11 male IC patients, five had previously undergone TURP and two had undergone simple prostatectomy ***(14)***.

4 Similarities in Clinical Presentation Between IC and CP

The presenting signs and symptoms of CP overlap considerably with those of IC (Figure 1). Voiding symptoms, pain with intercourse, ejaculatory pain, and pelvic pain can exist in both conditions, further precluding a clean clinical distinction between them (Table 1). The temporal appearance of various complaints further confuses matters. Although different patients' symptoms may wax and wane, only 7% of IC patients will initially describe the entire complement of symptoms that they will ultimately develop. Driscoll and Teichman ***(15)*** reported that the median time for total symptom manifestation was 2 yr and that most patients never exhibit all symptoms traditionally ascribed to either IC or CP. Forrest and Schmidt ***(16)*** found a similar pattern in their series of 92 men with cystoscopically proven IC: average duration of symptoms was 8.8 yr, with the most commonly reported initial complaint being mild suprapubic discomfort, which progressed over 2.5 yr to severe suprapubic discomfort, severe dysuria, and severe urinary frequency. Sexual dysfunction occurred in 60% of patients with painful ejaculation. Lower back pain, perineal pain and tenderness, and testicular pain ultimately developed in approximately 50% of patients. Anterior rectal wall tenderness on digital rectal exam, a finding that would lead many clinicians toward a diagnosis of CP, was one of the most common physical exam findings in this series of IC patients. We have found similar patterns of symptomatology in our own patient population ***(17)***.

Symptoms described by prostatitis patients parallel those of IC and may include dysuria, perineal, penile, suprapubic, bladder, or testicular or ejaculatory pain ***(18)***. Interestingly, CP patients with persistent ejaculatory pain may experience a wider range of symptoms and may be less likely to improve over time ***(19)***. Pain or discomfort with bladder filling remains the hallmark feature of IC but is not a prerequisite for a diagnosis of CP Nevertheless, discomfort with bladder

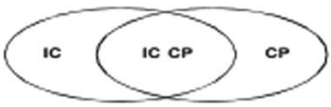

Fig. 1 Schematic Overlap between IC and CP

Table 1 Comparison Between IC and CP

	IC	CP
Symptoms	Urinary urgency, freq., pelvic pain, dyspareunia	Pelvic, perineal, testicular, penile, ejaculatory pain
Etiology	Neurogenic, autoimmune, effects of urine toxicity, occult organisms…	Neurogenic, autoimmune, effects of urine toxicity, occult organisms…
Pain with bladder filling	Almost always	45% of patients
Glomerulations with HD	Frequent	Frequent
Urine culture	Negative	Negative
Office cysto	No abnormalities	No abnormalities
Levator spasm	Frequently seen	Frequently seen
Signs of inflammation	Variable	Variable

filling is described in 45% of patients with CP ***(20)***. This figure is similar to a report by Mayo et al. ***(21)***, who found bladder hypersensitivity in 30% of patients with CP

IC rarely presents with detrusor instability, with between 0% and 14.6% patients demonstrating this finding ***(22,23)***. However, urinary hesitancy is a common complaint among patients with IC and CP The National IC Database Study noted this symptom in 78% of patients. This, in addition to complaints of poor urinary flow rates with interrupted voids, constipation, and generalized pelvic pain, strongly suggest associated pelvic floor pseudodyssynergia, or pelvic floor muscle spasm, broadly termed "pelvic floor dysfunction" ***(24–28)***. In our series of 100 IC patients meeting The National Institute of Diabetes and Digestive and Kidney Diseases criteria, patients presented with a decreased force of the urinary stream (75%), urinary hesitancy (75%), sense of incomplete voiding (73%), the need to strain with urination (70%), and lower back pain (43%). Eighty-one percent of these patients had levator ani tenderness on physical exam, the severity of which had a statistically significant correlation with the findings of constipation, decreased force of urinary stream, straining with voids, and urinary hesitancy ***(29)***. Most literature has demonstrated a high incidence of bladder neck and/or pelvic floor spasm specifically associated with the IIIB variant of CP ***(30–32)***. Hetrick and colleagues ***(33)*** found pelvic floor muscular abnormalities to exist in both Category IIIA and IIIB patients. Similarities between CP and IC were again seen in studies where 60% of CP patients were found to have glomerulations present after bladder

hydrodistention (a common finding in the IC patient) and 67% reported some symptom relief after the procedure ***(34)***.

5 Similarities in Pathogenesis Between IC and CP

Although studies of the pathogenesis of IC and CP have often taken divergent paths, they also reveal remarkable similarities. Some authors even argue that these syndromes represent urogenital manifestations of regional or systemic abnormalities, rather than organ-specific syndromes per se ***(35)***. In fact, Basken and Tanagho ***(36)*** report on four patients with chronic pelvic pain that persisted even after the creation of a urinary diversion and surgical removal of bladder, uterus, and fallopian tubes. Nonetheless, some of the popular and tenable theories of causation are discussed herein.

5.1 Occult Infection

Although the absence of bacterial pathogens is inherent to the definition of CP type III, inoculation with "atypical" or fastidious organisms has been proposed by numerous investigators ***(37–40)***. Shoskes and Shahed found bacterial DNA in as many as 70% of EPS specimens from patients with MCPPS IIIA, 57% of whom showed symptomatic improvement with antibiotic therapy ***(41)***.

Similarly, Ohkawa and coworkers demonstrated the presence of *Ureaplasma* in 18 of 143 (13%) chronic nonbacterial prostatitis patients ***(42)***. They also demonstrated the effectiveness of minocycline and ofloxacin in eradicating the organism in all 18 patients and achieving symptomatic improvement in 71.4%. These studies support trials of antibiotic therapy in treating CP patients despite the absence of laboratory-proven infection ***(43,44)***.

But the question remains of whether these bacteria were simply innocent bystanders while other processes were the true causation of pain. Keay and colleagues ***(45)*** demonstrated bacterial DNA to be present in the transperineal biopsies of 89% of prostate cancer patients, a greater percentage than that seen in the CP groups of other studies. Similarly, Nickel and colleagues ***(46)*** found the same bacterial count in the EPS of 463 CP patients as 121 age-matched controls. However, the former group had a significantly higher leukocyte count. Lee and colleagues ***(47)*** also failed to find any difference in prostatic bacterial growth between CP men and healthy controls. These conflicting data, difficulties in the determination of commensal versus virulent organisms, the focal nature of prostatitis, and the added variable of bacterial protection in the form of prostatic calculi and biofilms continue to confound investigative efforts.

An infectious etiology of IC has been sought by numerous investigators with disparate results, just as it has for CP Sophisticated culture techniques that identify fastidious or unusual bacterial forms, fungi, and viruses have failed to consistently

demonstrate a causative organism for IC ***(48)***. Similarly, PCR technique has failed to consistently demonstrate differences in bacterial forms between bladder biopsies of patients with IC and control subjects ***(49–51)***. Furthermore, a study by Warren *et al*. ***(52)*** showed no statistically significant difference in overall improvement between IC patients treated with a rigorous trial of sequential antibiotics and placebo.

Conversely, the findings of Potts and colleagues ***(53)*** do implicate a bacterial cause of IC. Even more striking than Ohkawa's finding of *Ureaplasma urealyticum* in 13% of the CP patients, Potts identified this organism in the urine of 48% of patients who would have been otherwise diagnosed with IC. Ninety-one percent of these patients treated with antibiotics experienced symptomatic improvement.

Another theory of IC pathogenesis implicates urothelial alterations that can result from bacterial cystitis. Many patients with IC have had a documented urinary tract infection prior to their abacterial bladder-based symptoms. Some authors contend that recurrent cystitis may cause permanent bladder injury ***(54,55)***.

5.2 Defective Epithelium

Another theory of IC pathogenesis pertains to an abnormal bladder surface. Bladder surface mucin (BSM) is the thin mucinous substance coating the healthy bladder. It is composed of varied sulfonated glycosaminoglycans and glycoproteins. Similar to the protective role of the mucous-layered gastric mucosa, BSM is thought to function as a bladder protectant, thereby mitigating the ability of organisms to bind to the underlying urothelial cells. Parsons and colleagues ***(56)*** propose that the breakdown of this mucinous layer, an entity dubbed transitional cell epithelial dysfunction, can lead to changes in permeability, stimulation of pain receptors, and inflammatory/hyperalgesia symptoms. The role of glycosaminoglycans and glycoproteins is underscored by the recent correlation of urinary glycosaminoglycan profile, urate content, and hyaluronic acid levels with IC symptom severity ***(57)***. Additionally, changes in urothelial markers related to urothelial impermeability and differentiation have been identified ***(58)***. Other changes of the epithelial surface identified in the IC patient include an augmented response to ATP secretion and upregulation of the ATP receptor subtype $P2X_3$ during stretch ***(59)***.

Could similar pathologies exist within the prostatic tissue of CP patients? Little is known about the surface characteristics of prostatic acinar tissue although, like the bladder surface, it does secrete mucin ***(60)***. Could changes in the prostatic acinar surface, coupled with the common finding of prostatic ductal reflux ***(61)***, account for pain?

Recent studies have also identified important differences between the urothelium of IC patients versus CP patients. Urinary antiproliferative factor (a low molecular weight glycosolated peptide produced by urothelial cells) activity is high for both male and female IC patients. Conversely, heparin-binding epidermal growth factor-like growth factor, another product of the urothelial surface, is found in low levels in the urine of these patients. Evaluation of CP patients for antiproliferative factor

activity and heparin-binding epidermal growth factor-like growth factor levels did not demonstrate any differences from controls. These data may have been influenced by excluding male patients from a diagnosis of CP if irritative voiding symptoms were present ***(62)***.

5.3 Neurogenic Inflammation

Neurogenic inflammation is a well-described event occurring in the IC patient as well as in other pain syndromes. One central component of this process is substance P, a short chain peptide that functions as a nociceptive neurotransmitter in the central and peripheral nervous systems, as well as a mediator of inflammation. When released by peripheral nerves (C-fibers or fibers associated with pain transmission), an inflammatory cascade results in processes such as mast cell degranulation and the activation of nearby nerves. The finding of increased numbers of substance P-containing nerves in the bladders of IC patients supports the role of neurogenic inflammation in IC ***(63,64)***. Likewise, an increased concentration of substance P has been found in the urine of patients diagnosed with IC, with the concentration of substance P proportional to the patient's degree of pain ***(65)***. The role of neurogenic inflammation in the CP patient has not been extensively studied.

5.4 Mast Cell Activation

Mast cells contain cytoplasmic granules, which contain substances such as histamine, leukotrienes, prostaglandins, and tryptases, all of which are mediators of inflammation. These granules may be released into the interstitium (degranulation) as part of an immunoglobulin E-mediated hypersensitivity reaction or in response to multiple other stimuli including neurotransmitters (substance P), cytokines, anaphylatoxins (complement: C3a, 4a, 5a), bacterial toxins, stress, and others ***(66–69)***. Mastocytosis has been reported in the bladders of 30% to 65% of patients with IC ***(70,71)***. This is probably an underestimation due to technical difficulties in identifying mast cells that have already degranulated ***(72)***. Further evidence of mast cell involvement comes from increased levels of histamine found in the bladder walls of patients with IC and increased urinary excretion of 1,4-methyl-imidazole-acetic-acid, a histamine metabolite, by these same patients ***(73–75)***.

Although little work has been conducted to determine the role of the mast cell in CP, case reports such as that submitted by Theoharides and colleagues ***(76)*** suggest that mastocytosis and elevated urinary histamine levels might be observed in some patients with prostatitis. This finding correlates well with an estrogen-induced model of prostatitis, in which increased numbers of degranulated mast cells were noted ***(77)***. This is corroborated by a histological study demonstrating a significant decrease in mast cell counts (as assessed by Toluidine blue staining) in

patients with prostatitis versus controls. Mast cells were fewer in number in the prostatitis group presumably due to mast cell degranulation ***(78)***. Increasing mast cell degranulation also appeared in the previously discussed rat model of spontaneous prostatitis with prostatitis progression.

5.5 Autoimmunity

Both IC and CP have many of the hallmarks of an autoimmune disease: symptom chronicity with exacerbations and remissions, frequent organ-specific mononuclear cell infiltrates, the lack of a clearly defined pathogen, occasional clinical response to steroids or other immunosuppressants, and the frequent finding of autoimmune inflammatory events ***(79,80)***. Unfortunately, studies investigating the role of autoimmunity in IC are far from conclusive and often conflicting. High levels of bladder-specific autoantigens have been identified in some IC patients ***(81)***. This finding, however, has not been consistently reproduced ***(82,83)***. Furthermore, some investigators posit that this phenomenon is simply an indirect response to local cellular damage, and is not itself a cause of the damage.

Similar controversy exists regarding the presence of autoimmunity in the patient with CP Alexander and colleagues ***(84)*** demonstrated that three of 10 men with CP had an autoimmune response to prostatic proteins, as evidenced by a T-lymphocytic response to seminal plasma. Batstone and colleagues ***(85)*** demonstrated a statistically significant heightened T-cell proliferative response to seminal plasma proteins in CP patients (13/20) compared with controls (3/20) ***(85)***. Although some patients with CP appear to have evidence of autoimmunity-related pathogenesis, autoimmunity may also be present in conditions as common as benign prostatic hyperplasia ***(86)***.

6 Diagnosis

IC remains a diagnosis of exclusion. The history, physical exam, and absence of other identifiable disease largely define IC and CP, yet the distinction between them can still be unclear (Table 1). Unfortunately, research criteria established by the NIDDK in 1988 (Table 2) have been used by some clinicians for diagnosis in the community setting. Hanno et al. ***(87)*** demonstrated that this practice may result in approximately 60% of IC patients' going untreated. Although most clinicians insist upon the presence of urinary frequency to accompany a diagnosis of IC, a recent publication by the American Urological Association (www.UrologyHealth.org) stated: "Many people have only pain and no frequency… There have been many reported cases when a person diagnosed with IC was not experiencing substantial pain." Nevertheless, it has been our approach to make an initial diagnosis on the basis of pelvic pain/discomfort associated with irritative voiding symptoms.

Table 2 The National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDK) IC Criteria

Inclusion criteria
1. Pain associated with the bladder **or** urinary urgency **and**
2. Glomerulations or Hunner's ulcer on cystoscopy
Exclusion criteria
1. Bladder capacity greater than 350 mL on awake cystometry
2. Absence of intense urge to void with bladder filled to 100 mL of gas or 150 mL of water during cystometry
3. Demonstration of phasic involuntary bladder contractions on cystometry
4. Nocturia < 2
5. Duration of symptoms <9 mo
6. Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics, or antispasmodics
7. Frequency of urination, while awake, of fewer than 8 times/day
8. Diagnosis of bacterial cystitis or prostatitis within a 3-month period
9. Active genital herpes
10. Bladder or lower ureteral calculi
11. Uterine, cervical, vaginal, or urethral cancer
12. Urethral diverticulum
13. Cyclophosphamide or any type of chemical cystitis
14. Tuberculous cystitis
15. Radiation cystitis
16. Benign or malignant bladder tumors
17. Vaginitis
18. Age <18 years

Gillenwater, J. Y, Wein, A. J. (1988) Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis. *J. Urol*. **140,** 203–206.

If therapy directed toward the chosen diagnosis is unsuccessful, consideration is given to diagnosis of the other condition (Figure 2).

Mandated laboratory testing includes a urinalysis. Recommended testing includes urine cytology, particularly in the patient older than 50 years of age and those patients with a smoking history. Urine culture and studies of prostatic secretions are performed depending upon the clinical circumstances.

Urodynamic evaluation may be helpful in those male patients in whom anatomical or functional obstruction is considered. Non-neurogenic detrusor-sphincter dyssynergia, which is characterized by contraction of the external urinary sphincter during voiding, can present with symptoms especially mistakable for CP or IC. Kaplan and colleagues ***(88)*** identified 43 such patients older than 16 yr who had initially been diagnosed with CP and who had been treated with antibiotics for an average of 67 days. Once the correct diagnosis was made, most (83%) of these men's symptoms improved with behavior modification and biofeedback ***(88)***. Because formal urodynamic testing can be quite uncomfortable for the male patient already suffering from pelvic pain, we recommend baseline uroflowometry and an ultrasound derived measurement of post-void residual volume as initial studies.

The value of cystoscopic examination is controversial as most examinations reveal no mucosal changes. Nevertheless, approximately 50% of IC patients who have Hunner's ulcer disease do not demonstrate either hematuria or pyuria on

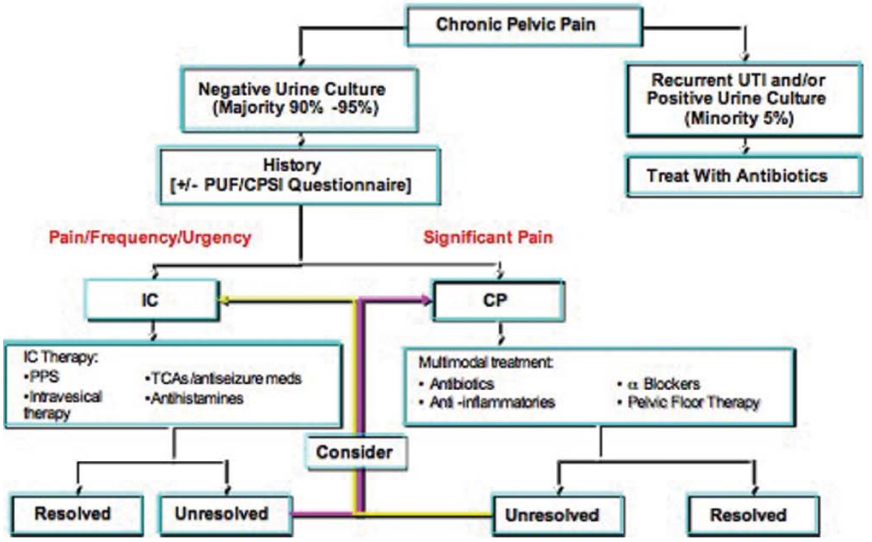

Fig. 2 Diagnostic distinctions between CP and IC

routine urinalysis. As these patients may respond to targeted therapies, we continue to include cystoscopy as a standard part of our evaluation ***(89)***.

Cystoscopy with hydrodistention has historically been the gold standard to better define the bladder as the source of the patient's symptoms. The technique is performed under general or spinal anesthesia, after which the bladder is filled with irrigant to 80–100 cm H_2O. Cystoscopy is performed during filling to identify any bladder tears that might develop during the filling process. Typical findings associated with IC include the presence of glomerulations (punctuate submucosal hemorrhages), mucosal tears, and/or a subnormal bladder capacity. Bladder biopsies are taken if mucosal lesions are identified. Although bladder hydrodistention may result in some symptom relief, a recent study demonstrated that only 36% of patients had more than 30% symptom relief one month after hydrodistention ***(90)***. Symptomatic improvement, when occurring, is usually short-lived. Furthermore, the role of hydrodistention has been questioned since no correlation has ever been established between a given patient's clinical presentation and hydrodistention findings ***(91–93)***.

The "KCl test" was initially described by Parsons as a relatively simple office procedure to help diagnose IC. The test entailed the intravesical administration of a 0.4 mmol KCl solution which, in the face of IC, would usually prompt irritative voiding symptoms and/or generate pelvic pain ***(94)***. The test was based upon presumed alteration of the bladder surface, which would facilitate KCl absorption, resulting in an enhancement of symptoms. Others argue that the results may be attributable to allodynia of the bladder surface. Parsons and colleagues ***(95)*** demonstrated that 84% of 43 patients with CP tested positive with the potassium sensitivity test. These investigators suggest that this finding, along with nearly

identical clinical presentation, makes any separation between IC and prostatitis both "artificial and arbitrary."

Intravesical instillation of anesthetic agents into the bladder (termed "anesthetic challenge") may play a role in IC diagnosis. A significant decline in pain after the instillation of a 1:1 mixture of lidocaine and 0.5% bupivacaine resulted in a greater than 50% reduction in pain in 74% of non-Hunner's ulcer IC patients ***(96)***.

7 Treatment

Treating IC and CP can prove frustrating for the patient and clinician alike, as no treatment regimen has demonstrated consistent efficacy. Interventions that provide relief to one patient may exacerbate the symptoms of another. And although no cookbook-type therapies exist, most patients and clinicians report most success from multimodal therapy. For these reasons, it must be impressed upon a patient that he must play an active role in understanding and appreciating his specific disease, its triggers, and its beneficial interventions. The importance of a productive physican/patient relationship cannot be underestimated here. Patients must be given realistic goals, which can often be accomplished by patient-to-patient communication and support groups and services, such as the Interstitial Cystitis Association (*www.ichelp.org*; 1-800-help-ICA).

7.1 Diet Modification

The substances listed in Table 3 comprise a partial list of those foods indicted by IC patients as aggravators of their symptoms ***(97)***. Because not all foods will bother all patients, patients should be encouraged to keep a diary of their food intake over a reasonable period of time, making notes of substances which alleviate and worsen their symptoms.

Patients often mistakenly decrease their fluid intake to limit voiding frequency. This, in turn, results in concentrated urine which appears to exacerbate symptoms. Patients, therefore, frequently need to increase their fluid intake. Smoking cessation, if applicable, should also be encouraged.

7.2 Behavioral Modifications and Physical Therapy

Some IC patients, especially those with milder symptoms, may respond well to a bladder retraining protocol using a continued delayed voiding technique. Bladder retraining is best accomplished when associated pain is controlled. Periodic voiding diaries may be helpful to monitor progress.

Table 3 Foods and Ingestibles That May Exacerbate IC and CP Symptoms

Aged cheeses	Chocolate	Pickles
Cranberries	Alcoholic beverages	Onions
Nuts (except cashews, pine nuts)	Fava beans	Junk foods Vinegar
Peaches		Soy beans
Chicken livers	Recreational drugs	Preservatives
Sour Cream	Monosodium glutamate (MSG)	Salsa
Grapes	Lima beans	Saccharine
Citric acid	Pineapples	Rhubarb
Yogurt	Plums	Caviar
Nectarines	Carbonated beverages	Sauerkraut
Benzol alcohol	Artificial sweeteners	Apricots
Allergy medications	Pomegranates	Anchovies
Tomatoes	Artificial ingredients	Mustard
Smoked meats	Fruit juices	Apples
Artificial colors	Sourdough bread	Caffeine
Mayonnaise	Smoked fish	Ketchup
Strawberries	Rye bread	Tobacco
Diet pills	Coffee	Tea
Tofu	Spicy foods	Avocados
Salad dressing	Cold medications	Miso
Citrus fruits	Soy sauce	Bananas

Shorter, B. The effects of foods, beverages and supplements on the symptoms of interstitial cystitis. Long Island Jewish Medical Center Department of Urology Research Year in Review, June 16, 2005

Manual physical therapy also offers significant promise as a treatment modality for both CP and IC. Based upon the hypothesis that pelvic floor myofascial trigger points are not only a source of pain and voiding symptoms but also a trigger for neurogenic bladder inflammation via antidromic reflexes, Weiss endeavored to establish the efficacy of treating IC with manual physical therapy. Patients underwent weekly or biweekly manual physical therapy for 8–12 wk, and progress was assessed via subjective questionnaires, as well as measurement of resting pelvic floor tension via electromyography. Seventy percent of IC patients in this series had moderate to marked improvement ***(98)***.

7.3 Oral Therapies

7.3.1 Pentosan Polysulfate Sodium (PPS)

PPS (Elmiron) is often used as first-line therapy for the treatment of IC, and remains the only oral medication approved by the Food and Drug Administration (FDA) for the treatment of IC. PPS is a synthetic glycosaminoglycan, very similar in molecular structure to the constituents of bladder surface mucin. One theory of IC

pathogenesis holds that a defect in this layer allows noxious urine solutes access to underlying tissue, thus beginning a cascade of nerve sensitization and/or inflammation. PPS's presumed mechanism of action is that it augments this layer, thus providing a gradual improvement in symptoms. In one study, 38% of those treated with PPS experienced >50% improvement in pain compared with 18% in a placebo group ***(99)***. A multicenter, double-blinded placebo-controlled investigation demonstrated that high doses of pentosan polysulfate resulted in statistically significant symptom improvement in CP patients as compared with those taking placebo (36.7% vs. 17.8%, respectively) ***(100)***. The efficacy of PPS in treating IC as well as CP further underscores the similarities between these two conditions. PPS is generally well-tolerated, with notable but uncommon side effects of reversible alopecia, GI upset, and derangements of liver function. Standard dosing is 100 mg three times daily. It may take months to reach its full efficacy.

7.3.2 Antihistamines

The inhibition of histamine release from mast cells can be accomplished with the use of antihistamines such as hydroxyzine (Vistaril or Atarax). Such agents must be prescribed judiciously, because they are sedatives and may adversely affect men with obstructive voiding symptoms. Dosing should begin at 10 to 25 mg qhs for the first week, up to a maximum of 75–100 mg. This medication may take up to 3 months to achieve its full efficacy. No placebo controlled studies documenting efficacy are available.

7.3.3 Tricyclic Antidepressants (TCAs)

TCAs, such as amitriptyline (Elavil), may also demonstrate efficacy in managing IC-associated urgency, pelvic pain and nocturia ***(101)***. This class of drugs acts as a central and peripheral anticholinergic, blocks reuptake of serotonin and norepinephrine, blocks sodium channels, and also has antihistaminic properties. Amitriptyline is usually administered nightly, taking full advantage of its sedating effects for the treatment of nocturia. At a mean follow-up of 19-months, Van Ophoven and colleagues ***(102)*** demonstrated a 64% response rate at a mean dose of 55 mg nightly. However, this group also observed a 31% dropout rate, largely because of the drug's side effects of fatigue, dry mouth, constipation, weight gain, decreased libido, and liver dysfunction. For this reason, treatment should be initiated only after pre-existing constipation has been treated. Treatment should begin at a low dose (10 or 25 mg nightly) and should be increased as needed. Like hydroxyzine, this medication should be used with caution in the patient with obstructive voiding symptoms. Also, because of its effect on cardiac conduction, amitriptyline should be used with caution in those patients with a history of cardiovascular disease.

7.3.4 Serotonin/Norepinephrine Reuptake Inhibitors

Many clinicians report success in treating IC and CP with selective serotonin/norepinephrine reuptake inhibitors. These drugs generally have few significant side effects and are well tolerated. Vanlafaxine (Effexor) (150 mg daily) is a reasonable option.

7.3.5 Antispasmodic, Antiseizure, and Muscle Relaxant Medications

These medications have been described to aid in the relief of the debilitating symptoms associated with IC. Anticholinergic agents may help those 15% patients with accompanying bladder overactivity. Gabapentin (Neurontin; 100 mg each day to 3600 mg in divided doses per day) and Pregabalin (Lyrica; 100–300 mg per day in divided doses) are antiseizure agents that are approved by the FDA for the treatment of neuropathic pain syndromes and may be helpful in the treatment of IC ***(103)***. The most problematic side effect from these agents is fatigue. Muscle relaxants such as diazepam (2–5 mg three times daily) may be helpful in the treatment of accompanying spasticity of the pelvic floor musculature.

7.4 Intravesical Therapies

50% dimethyl sulfoxide (DMSO; Rimso-50) is the only FDA-approved intravesical therapeutic agent for interstitial cystitis. Although its precise mechanism of action is unknown, its anti-inflammatory, analgesic, and muscle-relaxing properties appear to increase bladder capacity in many patients. DMSO may provide symptomatic relief in the majority of patients. However, repeated treatments are often necessary. Furthermore, the first several treatments may cause symptoms to flare.

Heparin sulfate (10,000 units in 10 mL of sterile water) also has been used successfully as an intravesical agent for the treatment of IC. Heparin sulfate is a normal component of the bladder's protective mucus layer. Like PPS, heparin's theoretical mechanism of action is an augmentation of the bladder's normal protective surface mucin, thus preventing noxious bladder solutes from stimulating the bladder surface. Parsons and colleagues reported clinical improvement in 56% of patients treated with intravesical heparin three times per week for 3 months, and continued remission for nearly all patients treated for 6 to 12 months ***(104)***. Others demonstrated the enhanced effects of a combination of DMSO and heparin compared with either agent alone ***(105)***. Relapse rates were reduced and duration of remissions was extended with this protocol. As noted in Section 6 ("Diagnosis"), the instillation of intravesical anesthetic agents can provide symptomatic relief.

7.5 Surgery

As a last resort, surgery can be used to ameliorate the most debilitating symptoms of IC. Hunner's ulcer fulguration and transurethral excision of ulcers have both offered symptomatic relief ***(106,107)***. Although not major surgeries, these therapies can result in clinical remissions. Unfortunately, however, long-term symptom relief is rarely achieved, and the ulcers tend to relapse. In nonulcerated patients, hydrodistention can similarly offer short-term relief. Hydrodistention in the face of Hunner's ulcer disease should proceed with extreme caution due to the high risk of associated bladder perforation and bleeding.

Many urologists are reporting excellent results with intravesical and intraprostatic botulinum A toxin injections for treating both CP and IC. Detrussor hyperactivity can be treated with cystoscopic injections into the detrussor of 80 to 200 units of Botox, whereas CP has been treated effectively with transperineal, transrectal, and transurethral injections. This therapy can last many months, and can be repeated when the efficacy begins to wane ***(108,109)***. Because Botox is not yet FDA approved for these purposes, the patient must pay for it out-of-pocket.

Neurostimulation with implantable electrical stimulators, such as Interstim, has proven beneficial in some series. Chai ***(110)*** reported a statistically and clinically significant improvement in voiding frequency, urgency, and pelvic pain in a small series. Other authors have subsequently shown Interstim to be efficacious for IC in control of symptomatic control and decreasing narcotics use in larger series ***(111–115)***. However, other series have failed to reproduce these results and, to our knowledge, prior series have included both men and women.

Subtotal or supratrigonal cystectomy with bladder augmentation (using a portion of detubularized bowel) is best performed in patients with severely diminished bladder capacities in the face of Hunner's ulcer disease ***(116)***. One must consider the high risk of chronic urinary retention and the need for long-term intermittent catheterization after this procedure. Total cystectomy or urinary diversion may also be considered for patients refractory to other conservative modalities. Patients must be thoroughly counseled preoperatively regarding the possibility of continued pelvic pain postoperatively.

8 Conclusion

Diagnosing and treating interstitial cystitis in men can prove to be an exquisitely challenging undertaking. The absence of established therapeutic regimens, predictable responses, or even objective measures of success makes this task an especially difficult one. The striking similarities between this entity and chronic prostatitis further obfuscate matters. As these important entities become better understood and more accurately characterized, the patients that they afflict will hopefully receive better and more durable treatment.

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Chapter 16
Category IV Prostatitis: Implications for Prostate Cancer Screening, Diagnosis, and Carcinogenesis

J. Stephen Jones

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Summary Category IV prostatitis is broadly defined as asymptomatic prostatic inflammation. It is present in large numbers of healthy men and is especially notable in men with elevated prostate specific antigen (PSA) and benign prostatic hyperplasia. The relationship of inflammation as a cause of elevated PSA is clearly established and as a potential cause of prostate cancer is supported by theory and a body of mainly preclinical evidence. In contrast to the theory that chronic prostatitis may increase the risk of future prostate cancer, it is also possible that this finding might explain elevated PSA in a man with an initial biopsy failing to identify prostate cancer. To date, this has been inadequately investigated, and the finding of inflammation on initial biopsy should not raise the threshold for repeat biopsy if clinical suspicion of prostate cancer persists based on elevated PSA, high grade prostatic intraepithelial neoplasia, or atypical small acinar proliferation.

Keywords: Prostatitis; inflammation; prostate; biopsy; prostate cancer.

1 Introduction

Category IV, or asymptomatic inflammatory prostatitis, is the least-investigated but perhaps most common of the subdivisions of prostatitis as defined by the National Institutes of Health consensus panel. It is defined by the presence of significant

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leukocytes, bacteria, or both in prostate-specific specimens in the absence of typical chronic pelvic pain. Initially, the category primarily considered inflammatory changes identified in expressed prostatic secretions (EPS) or semen in men with infertility or other presumably benign presentations (Figure 1).

This chapter addresses a potentially more common situation—asymptomatic stromal or glandular inflammation. It is unknown how many men have histological inflammatory changes in the general population, but it is exceedingly common among men who have specimens available for pathologic review. Such changes are often detected in histological specimens from patients suspected of having prostate cancer. Biopsy is usually based on elevated PSA, although occasionally induration identified by digital rectal examination can be due to painless inflammation. The other source of such tissue is from surgical specimens obtained through transurethral resection of the prostate, open, or radical prostatectomy.

2 Prevalence

Approximately one-third of patients (32.2%) screened for prostate cancer are found to have category IV prostatitis by EPS criteria if testing is performed (1). However, the true prevalence is difficult to define because most studies involving elevated

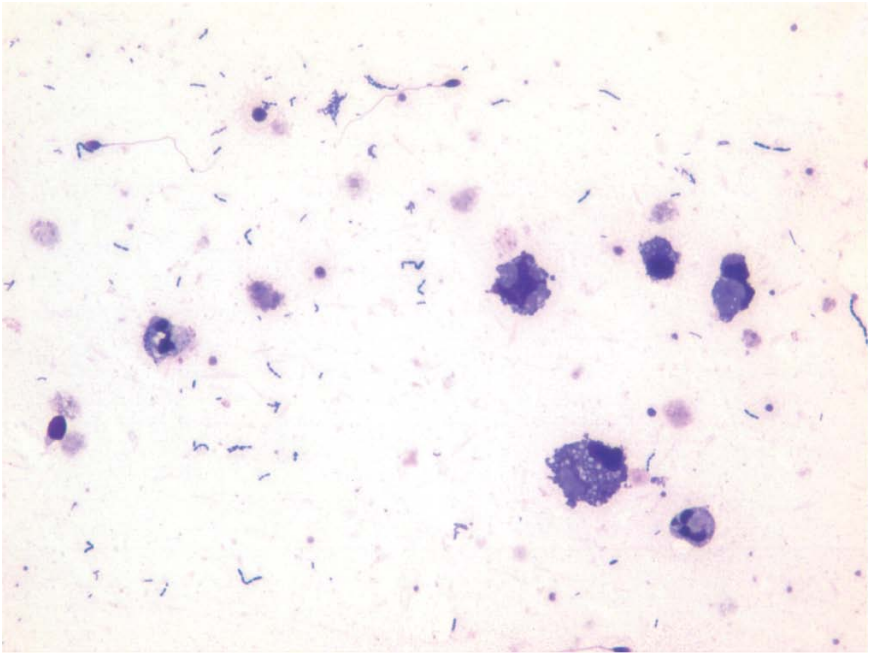

Fig. 1 WBC's can be identified in semen specim from a man with category IV prostatitis

PSA do not proceed to prostatic massage to test for prostatitis. Moreover, the Mears-Stamey 4-glass test has been largely abandoned; therefore, few men are ever tested for the presence of this condition that is unlikely to stimulate investigation based on its definition of being asymptomatic.

The largest project to consider the question, the Chronic Prostatitis Collaborative Research Network Study Group, performed serial 4-glass tests (VB1, VB2, EPS, VB3) on 463 men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and 121 normal controls. Men with CP/CPPS had greater leukocyte counts in their expressed prostatic secretions (EPS) and all segmented urine samples. However, semen values for inflammatory cells were similar in study patients and controls. Of the men with CP/CPPS 50% and 32% had 5 or more or 10 or more white blood cells (WBCs) per high power field in EPS, respectively. In comparison, these WBC levels were found in only 40% and 20% of controls. Patients with CP/CPPS had 5 or more or 10 or more WBCs per high power field in VB3 in 32% and 14%, whereas 19% and 11% in the control population had the same levels of WBCs. Positive EPS, VB3, and/or semen cultures were no more common in men with CP/CPPS (8.0%) than they were in asymptomatic men (8.3%). Conversely, in men with symptomatic CP/CPPS, the same collaborative group found poor correlation of EPS findings and symptom severity ***(2)***. The high prevalence of WBCs and positive bacterial cultures in the asymptomatic control population challenges the clinical usefulness of the 4-glass test as a diagnostic tool in men with CP/CPPS ***(3)***. These findings presumably reflect the incidence of category IV prostatitis among controls. However, because the EPS findings were less frequent than in the studies described below suggest may be the prevalence in the population, they might also call into question the diagnosis of Category IV prostatitis based on semen specimens alone. Thus, although the finding of inflammatory cells in prostatic fluid is the sine qua non defining category IV prostatitis, it appears that the clinical value of finding inflammation in prostatic fluids may be limited.

3 Pathophysiology

Prostatic tissue is theoretically sterile under normal circumstances, although retrograde entry of bacteria into prostatic ducts is well recognized. Data are limited because tissue cultures are rarely indicated, especially in the absence of clinical suspicion of infection. However, the use of polymerase chain reaction demonstrates microorganisms in the prostate gland of a majority of men with CPPS ***(4)***.

Findings suggestive of infection may be expected in symptomatic men, but uropathogenic bacteria have also been identified in tissue from many asymptomatic patients with a documented history of previously treated chronic bacterial prostatitis in whom EPS cultures became sterile after antibiotic therapy, suggesting that semen cultures underestimate the presence of bacteria ***(5)***. Moreover, immune complexes have been identified in the prostate of patients in the absence of positive tissue culture, suggesting that asymptomatic inflammatory changes in the prostate may be unrelated

to bacterial infection. These changes are often primarily located in the periurethral region, which is consistent with a theory of intraductal reflux of sterile urine.

Less investigation has been performed on men without a clinical history of prostatitis unless used as controls as above. However, men that have undergone prostate biopsy supply a voluminous amount of tissue for consideration of the prevalence of category IV prostatitis. Histological evidence of inflammation is routinely identified during biopsy for elevated PSA (Figure 2). Common in all reports, one study found inflammatory cells in every prostate biopsy specimen investigated ***(6)***.

Benign prostatic hyperplasia (BPH) has been purported to be highly related to inflammation. In a series of 176 transurethral resection of the prostate specimens, 98% were found to have inflammation ***(7)***. Thus, inflammatory changes in both semen and histological specimens are common findings that greatly exceed the clinical presentation of category I-III, or symptomatic, prostatitis.

Radical prostatectomy specimens contain inflammation in almost all cases, but it is unknown whether this has occurred because of or before the biopsy, which might induce inflammatory changes in the period between biopsy and prostatectomy ***(8)***. Our experience has been that inflammation is almost universal in radical prostatectomy specimens. In addition, we reported in a series in 2005 that chronic inflammation was present in 98% of biopsy cases, ranging from 0.2% to 44.6% of the tissue (mean 4.5%). Acute inflammation was present in 61% of the cases ***(9)***.

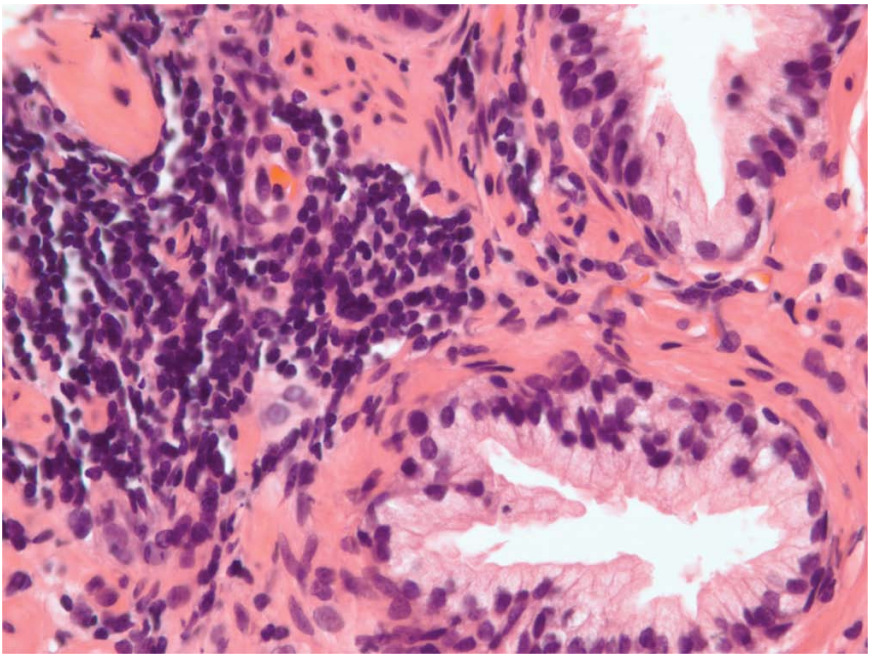

Fig. 2 Aggregate of lymphocytes adjacent to benign prostate glands, 40x magnification

Although category IV prostatitis is asymptomatic by definition, its status as a pathologic entity is difficult to characterize with these data. Men with an elevated PSA or BPH are often the source of pathologic material, but it is unknown whether asymptomatic men with a normal PSA have the same likelihood of harboring inflammatory histological changes. Autopsy data suggest that this may be a very common, if not normal, finding.

4 Impact of Inflammation on PSA

It is widely believed that inflammation causes an elevation of PSA by disruption of basement membranes in the tissue, allowing release of PSA that is subsequently detected in serum. This is described as a "leak" of PSA from prostate cells into the serum ***(10)***. An autopsy series of men without a pre-mortem diagnosis of prostate cancer found that 50% of those with inflammation had an elevated PSA >4.0 ng/dL, compared with 22% of those without inflammation, so the authors concluded that inflammation causes elevated PSA ***(11)***. The degree of inflammation was correlated with PSA levels in another study ***(12)***.

In a report of 376 men, the site of inflammation was highly correlated with increased PSA. Stromal, periglandular, and glandular inflammation did not increase PSA levels, but perivascular inflammation increased PSA levels significantly, suggesting that the mechanism of action requires immediate access to intravascular spaces ***(13)***.

The topic has been studied extensively in Asian men, where it has been proposed that inflammation increases the likelihood of a "false-positive" PSA reading. If this is true, it may be the cause of a higher likelihood of negative prostate biopsy compared with that likelihood in western men for similar levels of PSA. Results have been inconsistent. Kwak et al. ***(14)*** found no relationship between inflammation and PSA levels in 461 Korean men. Chang ***(15)*** found a relationship between the finding of inflammation and an elevated PSA in 223 men who underwent prostate biopsy, but did not find a relationship to the degree of PSA elevation. A Turkish study in 269 men found a strong relationship between inflammation and PSA, and recommended this guide the decision to perform repeat biopsy ***(16)***. Dublin reported experience in 131 Malaysian men regarding prostatectomy and biopsy specimens; the incidence of prostate cancer in patients with elevated PSA without concomitant inflammation was only 10%, compared with 60.5% in those with histological evidence of prostatitis ***(17)***.

Elsewhere, Simardi et al. ***(18)*** reported that the percentage of biopsy specimens involved with inflammation correlated with serum PSA levels in 51 Brazilian men. A French study in 66 men determined that it was not the extent of inflammation but rather the presence of inflammation associated with glandular epithelial disruption that significantly correlated with serum PSA level ***(19)***. A report of Arab men who underwent prostate biopsy found the incidence of prostatitis to be twice that of prostate cancer, 20.5% vs. 11% ***(20)***.

The duration of PSA elevation after a symptomatic episode of bacterial prostatitis has been shown in several small case series to last for several months. Game and colleagues ***(21)*** found that 1 to 2 months were required for most patients to return to baseline PSA following antibiotic treatment. PSA remained elevated in 39% of patients 3 months after treatment in a similar study by Kravchick ***(22)***. After febrile prostatitis, the changes have been shown to occur up to 6 months after treatment ***(23)***. During this asymptomatic interim, these patients could be liberally categorized as having category IV prostatitis.

The percentage of free PSA as a portion of total PSA was proposed as a method to differentiate benign versus a malignant cause of elevated PSA, but failed to provide a tool to distinguish prostate cancer from prostatitis. Both conditions are associated with a low percentage free PSA. A large study found that free and total PSA levels were affected similarly by prostate cancer and inflammation, but free/total ratio was different ***(24)***. The Chronic Prostatitis Collaborative Research Network noted that CP/CPPS is associated with a greater PSA level and that the percent free PSA is inversely correlated with inflammation, but concluded that PSA and the free/total PSA ratio were not valid as a biomarker to differentiate prostate cancer from CP/CPPS. Thus, they concluded that men with category IV prostatitis should be evaluated in identical fashion to men with no such history ***(25)***.

5 Impact of Inflammation on Carcinogenesis

Inflammation has been implicated in carcinogenesis for a number of malignancies, including prostate cancer ***(26)***. Animal models support the role of inflammation as a carcinogenic factor for prostate cancer ***(27)***.

Although the putative mechanism by which inflammation appears to increase the risk of prostate cancer remains unknown, possible mechanisms include the generation of reactive oxygen species, induction of cyclooxygenase-2, and release of paracrine factors that may lead to the induction or proliferation of cancer ***(28)***. Inflammatory atrophy has also been proposed as a potential precursor to prostate cancer ***(29)***.

MacLennan and colleagues ***(30)*** identified 144 men with inflammation identified during prostate biopsy and compared subsequent biopsy findings with those of 33 men with no inflammation on initial biopsy. They noted a strong association between serum PSA and the degree of inflammation. Cancer was identified in 20% of those with inflammation, compared with 6% of those without inflammation. They concluded from these findings that chronic inflammation may be a significant risk fact for prostate cancer. However, the series was small and weakly powered with 177 total patients, only 33 of which had no inflammation.

A much larger and more strongly powered but retrospective study of men with prostate cancer found that the relative odds of prostate cancer were elevated in men with history of any type of prostatitis (odds ratio = 1.7) or acute prostatitis (odds ratio = 2.5). The mean time from most recent episode of acute prostatitis to the

diagnosis of prostate cancer was 12.2 yr, and exclusion of men with acute prostatitis within 2 years before the index date reduced the relationship (odds ratio = 1.9). The impact appeared to be more related to significant infection than simply inflammation, as chronic bacterial prostatitis was more weakly associated with prostate cancer (odds ratio = 1.6). Chronic pelvic pain syndrome without suspected infection was associated with no increased risk ***(31)***. Based on the likelihood of category IV prostatitis increasing the risk of prostate cancer, inflammation presents a logical target for prevention strategies that are currently the focus of numerous investigations.

6 Treating Mildly Elevated PSA Before or Instead of Performing Biopsy

If inflammatory changes in the prostate cause an elevated serum PSA level that creates misleading concern for prostate cancer, it is logical that antibiotic administration might normalize PSA, obviating the need for biopsy. There are three major pitfalls in this logic. First, inflammation is not necessarily related to infection, and antibiotics will theoretically only affect the latter. Second, it is unknown whether the normalization of PSA truly rules out malignancy. Finally, the assumption that antibiotics are preferable to biopsy is intuitive but unproven.

Based on the goal of avoiding presumed unnecessary prostate biopsy, Potts ***(32)*** screened 187 men with elevated PSA levels (greater than 4 ng/mL) referred for urologic workup by testing for category IV prostatitis using prostate massage. Of the 122 patients that met the study criteria and agreed to undergo the study, 51 (42%) had EPS criteria qualifying for category IV prostatitis. These 51 men were prescribed 4 wk of antibiotics, and 22 had subsequently had normal post-therapy serum PSA levels (mean 2.9 ng/mL) and avoided biopsy. The investigator's conclusions were that screening for category IV prostatitis is effective and decreases the biopsy rate.

Bozeman ***(33)*** reported 95 men presenting with elevated serum PSA and who were diagnosed with chronic prostatitis based on evidence of inflammation in EPS. A 4-wk course of antibiotics and nonsteroidal anti-inflammatory drugs was administered, and serum PSA decreased by a mean of 36.4%. Almost half, 46.3% of patients had PSA decrease to less than 4 ng/mL. Antibiotic therapy led to PSA decrease in 80% of 61 patients Karazanashvili treated with antibiotics for the combination of elevated serum PSA, and inflammation in EPS ***(34)***. In a prospective trial, Lorente et al. ***(35)*** studied the effect of a 3-wk course of quinolones on patients with a history of lower urinary tract infections, normal digital rectal examinations, and elevated PSA, and found that their subsequent serum PSA tended to be lower than that of a control group not treated with antibiotics.

Bulbul and colleagues ***(36)*** treated 48 men with lower urinary tract symptoms and an elevated PSA level using a 2-week course of ciprofloxacin. Of these patients, 52% had a decrease in their PSA level (median 48%). Those with no change in their PSA level underwent biopsy and were found to have prostate cancer in 39%. However, those who did experience a drop in their PSA level did not undergo

biopsy, and this positive rate for those who did undergo biopsy is approximately that of routine biopsy series so appears meaningless.

The conclusion that such screening or empiric antibiotic treatment safely eliminates unnecessary biopsy in men who respond is enticing. However, it is almost assured that a certain percentage of those who avoided biopsy might have been found to have significant cancer on biopsy. The mean PSA levels achieved with antibiotic administration in the above studies were still in the range of 2.0 or greater that have now been clearly shown to be highly related to prostate cancer risk, especially in men younger than the age of 60 ***(37)***. As pointed out by Nickel in a commentary on the above study ***(38)***, to save an "unnecessary" biopsy for 22 men, 122 men (five times as many) underwent prostatic massage. This involved expense of the procedure in addition to additional laboratory testing, in addition to the discomfort of massage. The pain of this procedure has not been investigated, but the pain of prostate biopsy is typically in the "mild" range in all studies where biopsy was performed with a periprostatic block, so it is unlikely for vigorous prostatic massage to be much better tolerated than biopsy. Finally, an additional 51 of those also underwent 4 weeks of antibiotics (expensive and associated with allergies and other potential morbidity) and added blood tests and physician visits.

The quandary will be to determine whether a large number of men should undergo these examinations, massages, added tests, and medications to reduce the morbidity and costs associated with performing a relatively small number of "potentially unnecessary" prostate biopsies, and also whether the biopsies were appropriate avoided. Knowing that some of these men actually who avoided biopsy undoubtedly had cancer leaves some number of cases of prostate cancer undiagnosed. If these cases are of low biologic potential this might be favorable, or at least not harmful if careful surveillance is maintained. However, the numbers of men that will ultimately undergo delayed biopsies and/or harbor undiagnosed malignancies have not been factored into the above models to date.

7 Risk of Biopsy in the Setting of Prostatitis

If some percentage of cases of elevated PSA is caused by prostatitis, it is clear that there is the potential for infectious complications when biopsy is performed in that milieu. Biopsy has been shown to be associated with a 1–3% risk of infection in most series even when prophylactic antibiotics are administered ***(39)***. A contraindication to biopsy is untreated bacterial prostatitis. However, the risk of true asymptomatic infection with category IV prostatitis is unknown, and should be low if there is inflammation in the absence of bacterial colonization.

Although rare, there have been isolated reports of severe sepsis and occasional deaths from prostatitis performed in the setting of preexisting infection ***(40)***. Therefore, if there is clinical suspicion of ongoing infection, treatment must be complete prior to proceeding to biopsy.

8 Treatment of Category IV Prostatitis

Considering the limited data on defining category IV prostatitis, there is even less guidance in the peer-reviewed literature on treating this clearly defined but vaguely present "condition." By definition, category IV prostatitis is asymptomatic, so routine attempts at improving patient status are misguided. Even if identified during infertility evaluation, antibiotic approaches to infertility presumed to be due to prostatitis in the past provided limited value and have been largely abandoned ***(41)***.

Attempts to treat abnormal PSA believed to be related to category IV prostatitis are more complex to assess. As noted previously, PSA levels have been shown in multiple studies to respond to empiric administration of systemic antibiotics. However, with there being no data to support the assertion that this rules out prostate cancer, forgoing biopsy is difficult to justify. The philosophical quandary is whether to believe the initial elevated PSA or the depressed level after antibiotic therapy. Combined with the findings of the Prostate Cancer Prevention Trial showing that even many men with "normal" PSA levels may have cancer, it is impossible to determine that these men do not have prostate cancer without adequate biopsy ***(42)***.

Inhibitors of 5-ari have also been advocated for selected cases of symptomatic prostatitis, but their potential to eliminate category IV prostatitis remains unsupported by the literature ***(43)***. It is hoped that randomized controlled trials for all proposed approaches will provide the evidence necessary for clinical decision-making in the future.

9 Conclusion

Category IV prostatitis is broadly defined as asymptomatic prostatic inflammation. It is present in large numbers of healthy men, and is especially notable in men with elevated PSA and BPH. The relationship of inflammation as a cause of elevated PSA is clearly established, and as a potential cause of prostate cancer is supported by theory and a body of mainly preclinical evidence. In contrast the theory that chronic prostatitis might increase the risk of future prostate cancer, it is also possible that this finding might explain elevated PSA in a man with an initial biopsy failing to identify prostate cancer. To date, this has been inadequately investigated, and the finding of inflammation on initial biopsy should not raise the threshold for repeat biopsy if clinically suspicion of prostate cancer persists based on elevated PSA, high-grade prostatic intraepithelial neoplasia, or atypical small acinar proliferation.

Although it is enticing to administer antibiotics empirically to asymptomatic men with elevated PSA, normalization of its value does not rule out prostate cancer. Therefore, men with category IV prostatitis should be regarded as any other men regarding prostate cancer screening and consideration of prevention protocols.

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Chapter 17
The Role of Nanobacteria/Calcifying Nanoparticles in Prostate Disease

Jeffrey A. Jones, Neva Ciftcioglu, and David McKay

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Summary The etiology of nonbacterial prostatitis and chronic pelvic pain syndrome remain elusive and therefore therapy nonspecific, mainly targeting symptom reduction. If an etiology could be identified, then more specific therapy, targeting the source, could be developed. Acute and chronic prostatitis and other chronic prostate conditions are often associated with evidence of inflammation, either acute, chronic, or both, as well as development of other histologic findings, such as corpora amylacea, which contain calcium phosphate, aka apatite. There have been a number of chronic conditions/diseases that were originally classified as idiopathic or noninfectious, such as peptic ulcer disease, which were later discovered to be infectious in origin. Could such be the case for nonbacterial prostatitis and chronic pelvic pain syndrome (CPPS) Calcifying nanoparticles (CNP), aka nanobacteria (NB) are small (50–200 nm), self-replicating entities that can be found in animal and human serum, urine, and tissue and produce an outer shell of apatite. What is the likelihood that the CNPs are associated with the development of inflammatory conditions of the prostate and possibly in the development of chronic prostatitis and chronic pelvic pain syndrome? This chapter will examine the controversy surrounding NB/CNP, as well as the evidence for CNP association with human genitourinary diseases especially that of the prostate.

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Keywords Nanobacteria; nanoparticles; calcification; prostatitis; calcifying nanoparticles inflammation

1 Introduction

What role do nanobacteria (NB), aka calcifying nanoparticles, nanoentities, nano-organisms purported genus/species: *Nanobacterium sanguineum*, play in the pathogenesis of prostatic infirmaries? This is a question that many have not even conceived of, much less asked, even less researched. However, the question becomes increasingly intriguing as one examines the evidence for the existence of a previously unidentified infectious organism of the prostate, which could explain several current paradoxes, for instance, rampant inflammatory changes, focal or diffuse non-neoplastic proliferative nodules, frequent calcium apatite calculi, etc.

In this chapter, the evidence both in support of and the lack of thereof to date will be presented but without a definitive conclusion for NB as a prostatic pathogen. The evidence is strong that nanosized organisms exist; however, the readers will be left to decide whether nano-organisms have the potential to live within, infect, or cause disease of the human genitourinary system.

2 Background/Theoretical Considerations

The prostate is one of the most commonly diseased organs in Western men, and is responsible for millions of physician visits and billions of healthcare dollar expenditures annually ***(1)***. *Prostate* disease includes, but is not limited to: acute and chronic prostatitis (CP), prostadynia, chronic pelvic pain syndrome (CPPS), benign prostatic hyperplasia (BPH), and prostate cancer ***(2–4)***. CP/CPPS and BPH can occur in men beginning in adolescence, but are increasingly common as men age ***(2,5)***. Of the current consensus classification of prostatitis, all but type III.B-CPPS-noninflammatory have associated inflammatory findings ***(6)***. Especially intriguing are the types III. A-CPPS with inflammation and IV-asymptomatic inflammatory prostatitis, where significant prostate leukocytosis exists but no uropathogens are identifiable ***(6)***. So both BPH and CPPS have an association with inflammatory changes ***(7–9)***, but why? There are postulations of a number of causative etiologies from infections with non-culturable organisms to hormonal imbalances (testosterone:estrogen) ***(10)*** and even neuroendocrine factors as the driving cause ***(11,12)***. Still, despite decades of directed research, the etiology of prostate disease CP, CPPS, and BPH as well as prostate cancer for that matter, are poorly understood. There are multiple theories to explain the pathogenesis of BPH and CPPS. The potential etiological factors are listed as follows:

- Bacterial infection (11,13–17);
- Obligate intracellular bacterial or non-bacterial infection (chlamydia, uroplasma, mycoplasma, fungal, viral) (18–23);

- Auto-immune response or disordered immune response; possible nonmitigated postinflammatory wound healing response (8,24);
- Neuromuscular, psychogenic stress or physical injury problem (25–34);
- Other (uric acid metabolism disorder, prostate stones (ductal calculi), allergic response, etc.) (34–40).

Although a number of studies have sought to find an infectious agent to implicate in the pathogenesis of prostadynia, CPPS, and BPH, no consistent agent has to date been identified ***(41,42)***. Using the Meares/Stamey criteria, uropathogens are identified in <10% of CPPS patients, yet many respond to some antibiotic therapy ***(42)***. Why have clinicians and researchers attempted to identify an infectious cause? Most likely it has been driven by a near universal finding of either acute or chronic inflammatory reaction in the histologic sections of men with CP, CPPS, and BPH whereas normal prostate shows no to minimal inflammation ***(42)***. Nanobacteria are unique agents that cannot be detected with standard bacteriological methods. Is it possible that NB may be the instigators of prostatic inflammation in cases of prostatic disease when no organism is isolated?

2.1 Corpora Amylacea

Prostatic calculi, aka corpora amylacea, are very common, present in >30% of radiographic studies of the male pelvis and a greater rate in men undergoing ultrasound of the prostate for clinical diagnosis, and transurethral resection of the prostate for the treatment of lower urinary tract symptoms (LUTS) ***(35,43)***. Urologists commonly encounter these "calculi" in patients undergoing ultrasound for both symptomatic and asymptomatic lower male genital tract evaluations, as well as during the transurethral resection of the prostate ***(44,45)***. Could NB be the source of calcium deposition around and within zinc-rich secretions of the prostatic acini and ducts of BPH patients, and may even be the causative infectious agent of multiple prostatic diseases with unknown etiologies? Prostatic calculi (corpora amylacea) typically are either comprised mostly of laminated hydroxyapatite or have central apatite concentric layers surrounding an organic core, usually originating from desquamated acinar epithelium ***(46,47)***. As is discussed herein, NB create apatite (layered calcium phosphate) structures around individual organisms; is this purely coincidental in relationship to prostatic calculi?

3 Do Nanobacteria/Calcifying Nanoparticles/Nano-organisms Exist?

Evidence is accumulating for the existence of organisms <1 μm in size (typically 50–200 nm) ***(48,49)*** which grow, replicate, and colonize inorganic and organic material worldwide ***(50–54)***. There is even some limited data to suggest that these

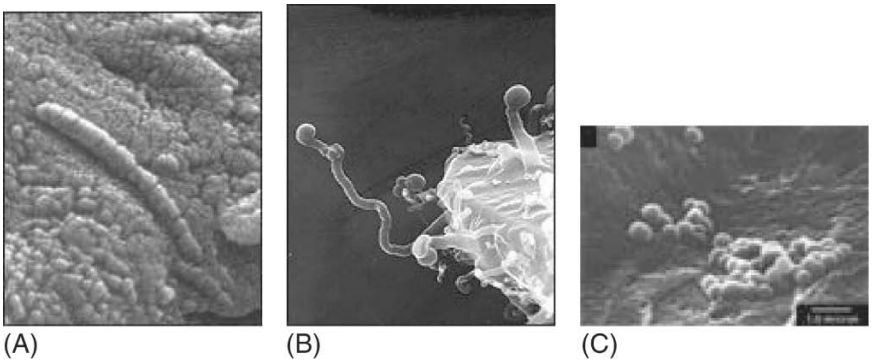

Fig. 1 **(A)** Allan Hills meteorite (scanning electron microscopy [SEM] image) **(B)** Nanobes on Jurassic/Triassic sand stones ***(61)***. **(C)** Nannobacteria on calcite (hot spring carbonate) as discovered by, Folk ***(54)***

organisms may exist extraterrestrially because of the presence of nano-fossils, with organic characteristics, in meteorites found in lunar and terrestrial sources, for example, the Martian meteorite ALH84001, from the Allan Hills of Antarctica which is of nearly irrefutable Martian origin, and the Allende and Murchison carbonaceous meteorites (Figure 1) ***(55–61)***.

3.1 History

Microorganism-like, minute spherical formations were first described in minerals by Robert Folk in 1990, when he discovered, while making a high magnification SEM study of hot springs carbonates. Those 25- to 200-nm scale spheroidal to ovoid-shaped objects were detected on the acid edged surface of the aragonite and calcite. Because these objects resembled smaller versions of coccoid *Streptococci* and *Staphylococci*, and because of their tendency to appear in chains or clusters, he initially proposed that the objects were "dwarf bacterial forms," about one-tenth the diameter of ordinary of bacteria, "nannobacteria." (Figure 1) Since that time, multiple additional investigators have reported finding these nanoparticles in a variety of locations ranging from meteorites, ice flows, and hydrothermal vents to human urinary calculi. Certainly prokaryotes as we know them can significantly reduce their size and cell volume into the size range of purported NB when placed under intense environmental stress ***(63,64)***. Marine and soil ultramicrobacteria can be found in sizes as small as 80 nm, with credible identified internal structures using transmission electron microscopy (TEM) ***(65,66)***. The relevance of those environmental nanoforms to the human pathology is not known; however, it is important to understand that nano-sized organisms are being found throughout nature, not only associated with human tissue. A phylogenic relationship between various nano-sized organisms has not yet been established.

The history of medically related ultramicroscopic organisms or elementary particles dates back more than 100 yr. Bechamp ***(52)*** claimed to have found "microzymas" in the body in the 19th century, and Lister found "Granuligera," minute urine granules that grew by dividing into four units (fissiparous generation) in 1875. Bacteria that could pass through ultra-fine filters were described as early as 1928 by Rivers, perhaps even earlier by Kendall and Hadley ***(52)***. So the existence of extremely small (submicron)-sized entities associated with diseased humans and their body fluids is not a new phenomena.

However, the notion of the existence of a genus/species of organisms in the nanometer size range (1/10 to 1/1000 the size/volume of conventional bacteria, but larger than viruses, i.e., 10–20 nm), is not without detractors. Many question the ability of such organisms to have adequate cellular machinery, (nucleic acids, ribosomes, etc.) to comprise bacterial life ***(67)***. In fact, critics of the assertion state that NB are below the size constraint for a living cell ***(68–70)***. There is also a lack of consensus of an appropriate taxonomy for such organisms, much less an understood pedigree for location of NB on the tree of life ***(71)***. Some critics have suggested that perhaps the observed calcific structures are in fact inorganic (geologic-like) processes ***(62,72)***, for example, crystalline precipitation, micromineral inclusions or crystallographic edge effects ***(73)***, or perhaps byproducts of free radical damage in or on cellular surfaces ***(71)***.

Multiple investigators, for instance, Robert Folk of the University of Texas and Phillipa Uwins of Queensland, Australia, have observed volcanic rock/soil derived nano-sized organisms with replicating properties underneath the microscope, although in Uwins' case, she prefers to call them "nanobes" because of a lack of understanding of their evolutionary development ***(61)***.

In 1998, Kajander and Ciftcioglu reported the isolation of NB from human blood, cow blood, and commercial blood serum preparations and describe the coccobacillar formations by NB of microscopic mineral structures (Figure 2) composed of apatite, a calcium- and phosphate-containing mineral at physiological conditions ***(49)***.

They advanced this process of "biomineralization" as a possible cause of pathological calcification in humans such as the formation of kidney stones ***(74)***. The scientists produced NB and their associated mineral structures in a medium containing 10% serum, which served as the presumed source of the NB inoculum. Control cultures prepared with gamma-irradiated serum were free of NB ***(75,76)***. Apatite formations generated during culture resembled flattened hollow spheres with an opening facing the bottom of the culture dish which, the discoverers stated, are "apparently the dwelling place of the organisms" (Figure 3). During a 1-month period of NB, cultures formed calcified biofilm formations at the bottom of culture vessels (Figure 4).

The Finnish team developed culture and detection techniques involving NB-specific monoclonal antibodies for this unique agent ***(75,76)***. By following the developed methodology, other independent scientists detected NB on such diverse conditions as arterial heart disease, Alzheimer's disease, kidney stone formation, polycystic kidney disease and malignant tumors ***(51,74,77–81)***.

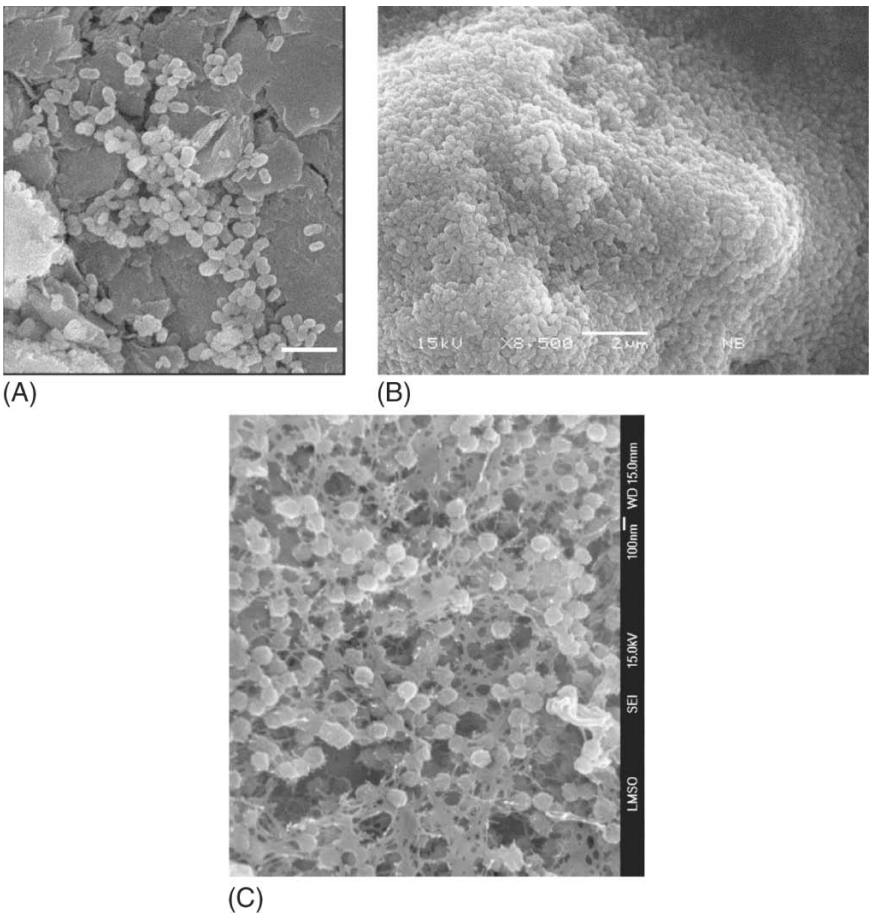

Fig. 2 **(A)** SEM image of small coccobacillar NB isolated from bovine blood. White bar is 1 μm. **(B)** SEM of replicating NB colony; White bar is 2 μm. **(C)** SEM image of small coccobacillar forms embedded in biofilm in samples from a carbonate precipitates in a hypersaline lake in the Caribbean. (Courtesy Monica Byrne). Although it has not been shown that these forms are remains of living organisms, nor any relationship to the human isolates, they are similar in appearance and fit many of the geologic criteria: spherical bodies, extremely close to each other in size (well sorted), completely embedded in an obvious biofilm

3.2 Properties of NBs

NB calcify, that is, form apatite, at physiologic conditions (neutral pH) and have been isolated ***(53,74,82)*** from human ***(75)*** and bovine sera ***(48)*** kidney cyst fluids from patients with polycystic kidney disease ***(80)***, demineralized kidney stone extracts ***(74)***, and in human sclerotic carotid arteries and aorta at autopsy ***(83,84)***. NB have been observed to be cytotoxic to fibroblasts *in vitro* ***(76)***. Despite the

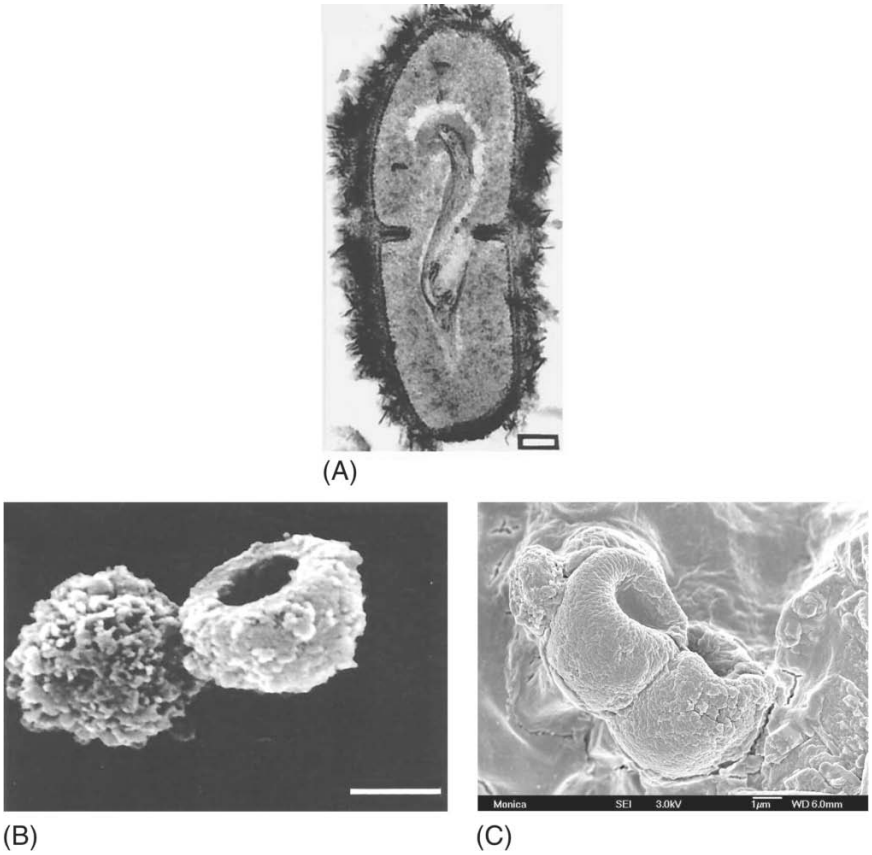

Fig. 3 **(A)** Transmission emission microscopy (TEM) of a dividing NB with apatite shell. **(B)** SEM of "igloo" formed by, NB. **(C)** SEM of two "igloos" formed by bacterial-driven precipitation in carbonate products of hypersaline lake in the Caribbean (Courtesy of Monica Byrne)

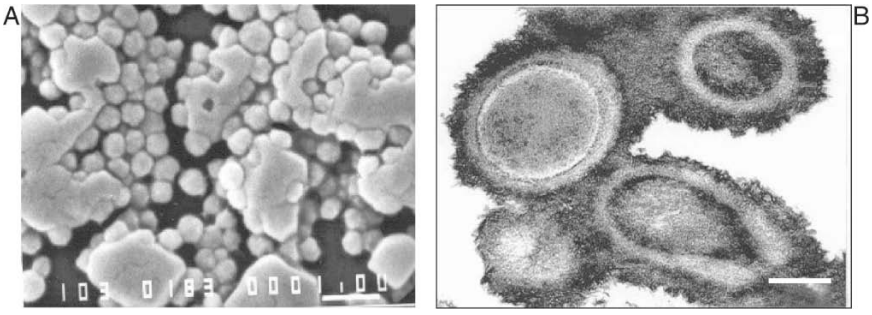

Fig. 4 SEM image of biofilm formed by NB (**A,** bar is 1 μm), TEM image of the calcified biofilm (**B,** bar is 100 nm)

duplication of these findings, all or in part in several laboratories ***(72,79,85–88)***, NB remain controversial entities due in part to their novel properties of small size (0.1–0.5 µm), slow growth (replication times of 1–3 d), difficult culture technical requirements (require mammalian cell culture conditions), atypical morphology, apatite coat, and resistance to extraction of its component parts by conventional methods (Table 1).

NB have different physical appearances during their life cycle and can change physical form during their growth and development. In one form when the organisms are cultured in 10% serum-containing cultures, their size remains between 50–300 nanometers ***(48,49)***, as seen in Figure 5.

Each NB accumulates calcium and phosphate and forms a calcific biofilm around itself that provides protection as well as provides a lattice for multiple NB to connect, communicate, and function together as a unit or colony. This calcific biofilm ***(89)*** allows the NB to expand, contract, and move collectively ***(90)***. In an other form, when NB cultured in serum/protein free conditions the calcific shell around themselves become thicker (up to 10 µm), they may remain relatively dormant, in a so-called "apatite-igloo," (Figure 3b) or they may aggregate into clusters with observed budding (Figures 3 and 4). So this biofilm-phase of NB life is commonly observed when they are reproducing but also when under environmental attack or physiological stress ***(53,76)***. The calcific biofilm ***(91)*** that is accumulated by the NB is an "endotoxin" and mediator (cause) of inflammation and swelling. The host can mount a response to the presence of this NB-secretion with swelling and irritation, release of cytokines, interleukins, leukocytes, mast cells, collagenase, matrix metalloproteinases (MMP), etc. The host reaction is to wall off the area of NB occupation. When NB are physically walled-in, they

Table 1 Unique Properties of NB With Respect to Bacteria and Virus (modified from *J. Clin Microbiol*. **41,** 3460–3461, 2003)

Properties	Bacteria	Nanobacteria/Calcifying Nanoparticles	Virus
Size	>250 nm	50–300 nm 500 nm-10 µm when extensively calcified	20–250 nm
Self-replication (speed)	+ (in minutes)	+ (in days)	–
Calcium phosphate deposition as a "cell envelope"	–	+	–
Multiplication characteristics	Binary fission	Binary fission and budding	Intracellular
Biofilm formation	+	+	–
Nucleic acids	+	No genomic DNA isolated	+
γ and UV irradiation resistance	–	+	–
Resistance to boiling temperature	–	+	Some
Lipopolysaccharide content (gram negative)	+	+	–

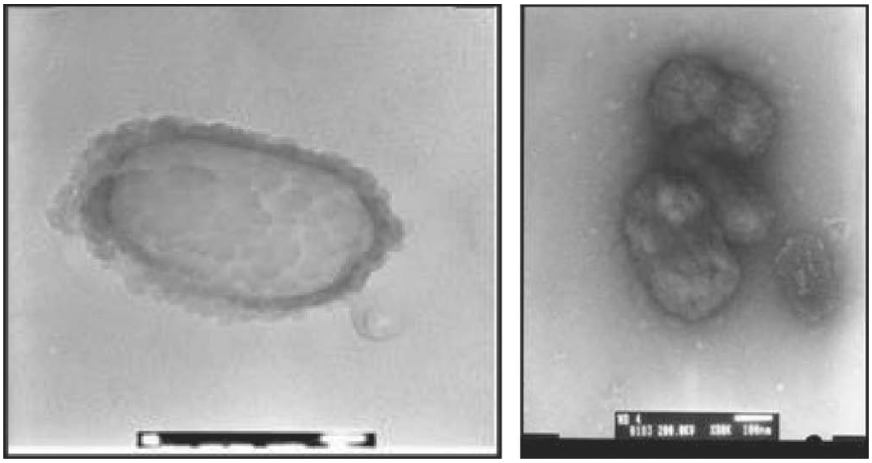

Fig. 5 TEM section of one small NB cell, coated with dark, apatite layer (left). Bar is 50 nm. Negative staining of small NB showing the grainy inner structure under TEM (right). Bar is 100 nm

cause chronic inflammation and swelling. Most of the commonly known medical "markers of inflammation" (C-reactive protein, MMP, interleukins, etc.) are found to be elevated in response to the "antigenic-endotoxin" in the NB biofilm ***(51,75,82,92,93)***.

Although nonbiogenic apatite is thought to be not immunogenic and thus useful as support materials in orthopedics and dentistry; Infection with NB (i.e., biogenic apatite) yields a host immune response ***(94)***. As seen in Figure 6, both cultured in vitro B, and NB apatite clusters in kidney stones has similar calcium phosphate composition. NB have been observed killing T lymphocytes and NK cells in the process of inducing a chronic inflammatory reaction. As discussed by Wainwright ***(52)***, NB are conceptually related to ultra-small microbes in medicine and the environment.

Whether NB themselves serve as the nucleus for crystal formation, or whether the NBs are simply able to lower the activation energy barrier and thus allow precipitation and growth of crystals under much lower super saturation conditions is yet to be determined. However, it is immaterial whether or not they are bacteria, viruses, or other living or nonliving forms; their properties of promoting ready crystallization and growth of calcium minerals are well established. These self-replicating particles may induce calcification and stone formation *in vivo* because NBs 1) have been detected in human blood, 2) are transported from blood into urine and bile as living organisms, 3) are renotropic, 4) cause apoptotic cell death, 5) are present in human stone-isolates and tissues with calcification, and 6) cause kidney stone formation in rats within 1 month when injected in an intrarenal route ***(51)***.

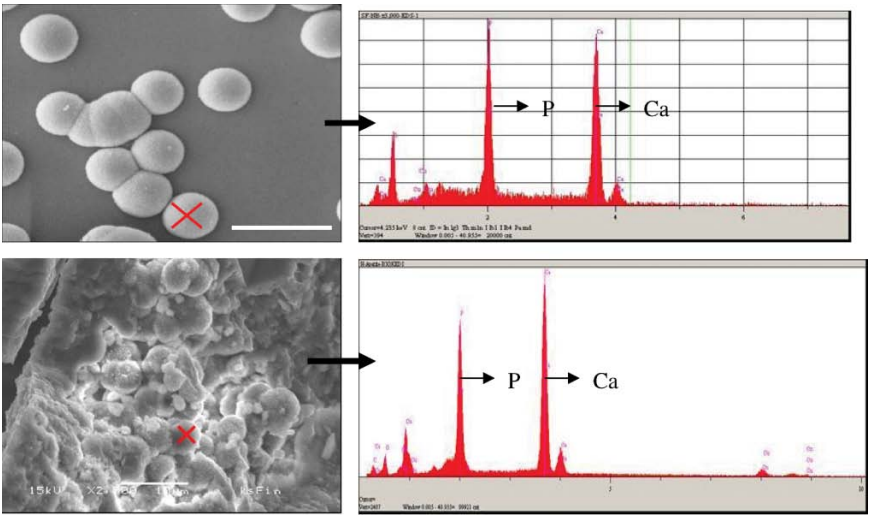

Fig. 6 SEM images of extensively calcified "NB igloo" after culturing in serum-free conditions. Small-sized NB were shown to be localized inside those clusters with TEM. Bar is 10μm. (upper left), and its EDS analysis showing Ca and P content of one of the sphere (igloo) marked with X (upper right). The down-left is the SEM image of spherical apatite (calcium phosphate) formations in the core of a calcium oxalate kidney stone (Bar is 10μm) , and its EDS analysis showing Ca and P content of one of the sphere (lower right) marked with an X

4 In Vitro/Histologic Evidence

4.1 Genitourinary-Prostate/Testes

4.1.1 Preliminary Data

There are numerous reports of observed inflammation in the prostate in BPH tissue samples and primary cell cultures, suggesting an infectious or autoimmune component ***(8,24)***. Preliminary studies by Ciftcioglu, et al have applied immuno-histochemical staining to paraffin embedded tissue samples in eight patients who were diagnosed with "testicular microlithiasis" and to three control testicular tissues ***(144)***. In this small pilot work, Ciftcioglu and colleagues used NB-specific monoclonal antibodies as the primary antibody. All the calcium deposition areas in the tissue were stained positively in all testicular microlithiasis samples, whereas the controls remained negative. Previous screening was performed for the presence of NB antigen in urine samples collected after prostate massage from prostatitis patients in Kuopio Hospital/Finland. Six of 10 samples tested were found to be NB-antigen positive.

Multiple conference reports from investigators performing primary prostate epithelial cultures have revealed difficulty in maintaining cellular viability and passage when using fetal calf or bovine serum (FCS, FBS) as a source of growth factors,

driving researchers to develop a serum-free media to support prostate epithelial cell growth ***(95–98)***. With standard filtration sterilization, NBs have been found in FCS via both microscopic inspection and culture techniques in 80% of lots tested. NB-infected mammalian cells show characteristic cytoplasmic inclusions, and such inclusions have been observed when attempting to establish primary prostatic epithelial cultures to be grown with FCS, but the inclusions were thought to be part of a cellular senescence process.

4.2 NB Prostate: Histologic

Positive staining for NB antigen in histological sections of prostates with a pathological diagnosis of BPH and to a lesser extent with prostate cancer has been reported (Figures 7 and 8) ***(99)***. Therefore, some data would suggest that NB particles, as measured by antibodies directed at unique NB antigens, at least colonize human prostate tissue. The immunohistochemistry staining was positive for NB antigen within the stroma, ducts and epithelial acini of the human prostate of patients with BPH, but to a lesser degree in patients with no clinical diagnosis of the prostate or prostate cancer.

4.3 Other Genitourinary (GU) Organ Involvement With NB

4.3.1 Kidney

A potential unifying principle for calcific-diseases of the genitourinary(GU) system includes infection/colonization with NB ***(99,100)***. Bacteria have a well-recognized role in the formation of specific type of renal lithiasis, magnesium ammonium phosphate, aka struvite, so it should not be a profound stretch of the imagination to

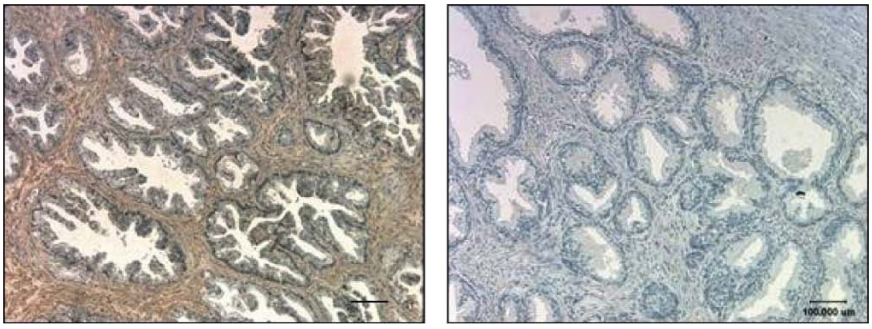

Fig. 7 Immunohistochemical staining (CSA) results of paraffin-embedded prostate tissue. Monoclonal antibody is NB-specific 8D10. Left, BPH; right, healthy prostate tissue. Brown color is the indicator of a positive CSA result. Bars are 100 μm

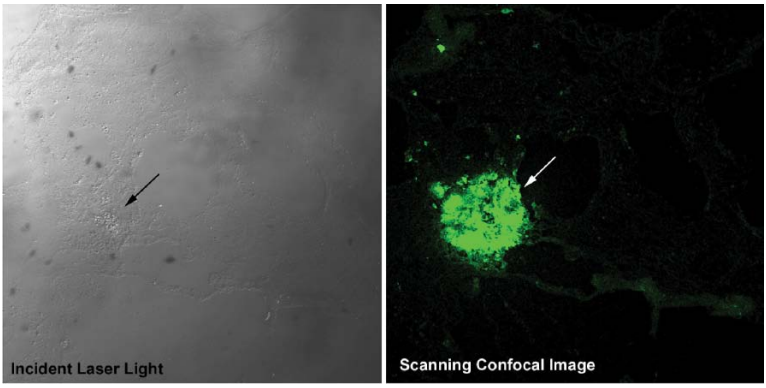

Fig. 8 The fluorescein image on the right depicts primary antibody staining in a frozen section of a prostate cancer section stained with NB primary antibody disclosed using an Alexa 488 goat anti-mouse IgG secondary antibody and viewed using a scanning confocal microscope (one micron optical section). Positive staining of discrete areas (arrow) within the section can be seen. These areas appear to have a different appearance (arrow) than the surrounding tissue under incident laser light (an approximation of phase contrast microscopy) on the left

consider an infectious etiology for at least some, if not all of calcium-based calculi ***(78,101,102)***. Multiple investigators have reported an association of NB with urinary lithiasis ***(74,88,100,103,144)***, including one report of 62% positive rate for apatite-forming, gram-negative, coccoid, ultrafilterable (60–200 nm) microorganisms in stones retrieved from 65 clinical patients (Figure 6) ***(94)***. There are others, however, with negative reports for NB and urinary stones ***(104,105)***. Studies are underway currently by researchers at NASA/Johnson Space Center and the University of California San Francisco to evaluate the role of NBs in the formation of Randall's plaques in renal pyramids.

A group from India have provided independent verification of earlier studies from the Finnish group ***(74)*** by injecting NB into Wistar rats and observing accelerated biocrystallization of 14-C-labeled calcium oxalate and formation of renal tubular calcification in animals receiving the NB ***(88)***. There are also researchers that feel, based on their studies, that NB contribute to the pathogenesis of PKD calcifications ***(80)*** and other renal diseases with associated vascular calcifications ***(106)***.

4.4 NB Potential Involvement With Disease in Other Organ Systems

4.4.1 Cardiovascular

For more than two decades, an infectious etiology for atherosclerosis has been sought, with the primary focus being the Chlamydia organisms, due mainly to

findings of positive ELISA testing for *Chlamydia pneumoniae* in atherosclerotic patients, even though the organism has not been cultured from the plaque itself, nor have results obtained with polymerase chain reaction for Chlamydial nucleic acid been positive. However, recently it has been discovered that NB often give "false positive" immuno-staining results with specific monoclonal antibodies for *Chlamydia pneumoniae* ***(51)***. Could NB be an infectious contributor to the formation of atherosclerosis?

A number of investigators in the last 5 yr have reported involvement of NB with disease of the cardiovascular system, including atherosclerotic plaque and valvular calcifications ***(83,84,107,108)***. Investigators ***(77)*** at the Mayo Clinic recently found, by immunostaining with the 8D10, NB-antibody, in postmortem specimens of arterial plaques, aneurysms, and valves, that NB-sized (30–100 nm) spheres were present only in the calcified sections. Interestingly, after decalcifying the spherules, they were recognized by DNA-specific dye and under electron microscopic inspection, appeared to have cell walls.

NB have been reported, at the 101st general meeting of the American Society for Microbiology, 5/23/2001, to be a contaminant in previously assumed sterile medical products, for instance, IPV polio vaccine. Many human biological products and vaccines are cultured in fetal bovine serum, a medium that is also reported to be contaminated with NB ***(75)***.

4.4.2 Cancer

Several scientists have reported finding evidence of NB association with neoplastic tissue of the ovary and breast ***(109,110)***, possibly involved in the formation of the commonly observed psammoma bodies, found in ovarian and thyroid cancers ***(110)***. There is even a report of NB contribution to the calcifications found in the fibrous capsule surrounding an implant after breast reconstruction ***(111)***. NB are being linked to a number of other human cancers, including leukemia ***(52)*** and nasopharyngeal carcinoma ***(112)***, although there is no current evidence for cause and effect in any of these reports.

4.4.3 Other Organ Sites

NB have been implicated in a host of diseases throughout the human body to include musculoskeletal issues ***(113)*** and arthritis ***(114)***, dental and periodontal problems ***(115,116)***, cutaneous disorders ***(117)***, black pigment gallstones ***(118)*** and bile ***(119)*** and sarcoidosis ***(120)***. Unexplained calcifications found in atherosclerotic plaque, coronary artery disease, urinary calculi, PKD, cataracts, scleroderma, psoriasis, eczema, lichen planus, hepatic cysts, breast disease-benign and malignant, corpora amylacea, dental plaque and periodontal disease, rheumatoid arthritis, osteoarthritis, fibromyalgia, osteophytes certain cancers, blood disorders, and myelodegenerative disorders such as multiple sclerosis, amyotrophic lateral sclerosis and Alzheimer's

disease all have all been theorized to be related to NB infection; and all due to an idiopathic pathological calcification process. Some researchers hypothesize that NB are the root cause behind all pathological calcification in humans and mammals. NB could provide a unifying theme behind many degenerative disease processes. Yet to date, there is not adequate scientific evidence to validate the preliminary findings in these many organ systems.

5 Nanobacterial Therapy

From what is known, destruction of NB is not an easily accomplished feat, at least with conventional antibacterial approaches. NB are extremophiles and have adapted to survival in harsh environmental conditions. They can survive exposure to freezing, dehydration, heat up to 90 °C, alcohol, peroxides, high frequency sonic generators, and γ-irradiation less than 30 kGy. They are not killed by penicillins, cephalosporins, macrolides, most other antibiotics, other bacteria or viruses, colloidal silver, lactoferrin, colostrum, or immunoglobulins.

Current evidence would suggest that treatment of a NB infection first requires removal of the protective calcium shells and then exposure to a cidal agent, specifically effective as an antinanobacterial. There are several proposed means to affect the biogenic apatite shell, including ethylene diamine tetraacetic acid and other chelators, as well as the bisphosphonates. There are numerous reports of strategies to safely deliver therapeutic systemic chelation treatment, albeit controversial, although currently advocated by alternative medical specialists ***(121–124)***. There are several routes for delivery of chelators, although it is felt usually that oral routes are less effective and instead intravenous or rectal routes are used clinically ***(121–124)***. Maniscalco and Taylor treated 77 patients with atherosclerotic cardiovascular disease (ASCVD), who were all positive for NB antigen, with the comET regimen (see description below) combining chelation with antinanobacterial antibiotics and found that 44 (57%) had a reduction in their coronary artery calcium scores, by a mean of 14% reduction. In addition, of 19 patients with angina, 16 (84%) had reduction or elimination of their symptoms. Lipid profiles were also improved on comET in the 86% of patients who had been receiving statin therapy ***(125)***.

Others have proposed that the calcium apatite shell around NB may be affected by the bisphosphonate-class of therapeutics, currently employed for the treatment of osteoporosis as well as carcinoma metastatic to bone ***(126–132)***. The mechanism of action for such a therapeutic has not been demonstrated because bisphosphonates seem to act by binding preferentially to the resorptive surfaces of bone, where they coat the hydroxyapatite crystal. In the presence of acidity, bisphosphonates are released from the bone and act to inhibit the activity of bone-resorbing osteoclasts ***(133,134)***. Bisphosphonate treatment thereby reduces bone turnover (i.e., activation frequency, or the rate at which bone remodeling sites are activated) and bone resorption at remodeling sites by their action on osteoclasts ***(133–135)***. Perhaps bisphosphonates could act in a similar fashion on NB to retard their production of

biogenic apatite. Yet, Silay and colleagues ***(136)*** have suggested that treatment of calcific atherosclerotic lesions with bisphosphonates may act by cidal properties of the agent on NB directly.

6 Clinical Evidence for Prostatitis Treatment

At least one investigative team has applied the concept of NB as a pathogenic entity for clinical therapeutics ***(137)***. Shoskes et al. ***(137)*** treated 16 men with category III CPPS of at least 9 months; duration that was refractory to multiple prior therapies, with a regimen of comET (Nanobac Life Sciences, Tampa, FL) consisting of 500 mg tetracycline and a proprietary mixture of ethylene diamine tetraacetic acid and a mixture of nutriceuticals, including ascorbic acid, coenzyme Q10, quercetin, selenium, grapeseed extract, hawthorn berry, L-arginine, B-vitamins 3, 6, and 9, L-lysine, L-ornithine, trypsin, and papain.. The men were evaluated with pre- and post-therapy National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI) scoring, blood and urine testing for NB antigen and transrectal ultrasound. Before treatment, 20% of the men in the authors practice fulfilled all of the inclusion criteria for comET therapy, including failure of anti-inflammatory regimens. 50% of the men had significant prostatic calcification prior to therapy. 60% of this select cohort had blood and 40% urine, positive for NB antigen. After 3–4 months of comET treatment, 53.5% ***(8)*** of patients had >50% reduction in symptoms, and 26.7% ***(4)*** had a 25–50% symptom improvement. Three patients (20%) had little (<25%) to no improvement; however, two of the three patients with minimal improvement interestingly had negative NB antigen testing, and all three had high NIH-CPSI urinary symptom scores and low pain scores. A total of 50% of patients with identified prostatic calculi had a reduction or resolution in calcification after comET treatment was completed ***(137)***. Of note, side-effects from the comET therapy were minimal, as there was no grade 3 or 4 toxicity reported.

7 What Is Missing? Research Needed

First, regarding NB, incomplete characterization of the organism has fueled a substantial debate, often based on speculation, rather that scientific evidence. A more thorough evaluation of the biogenic apatite formation around these organisms, using tools such as X-ray spectromicroscopy ***(138)***, confocal 3-D microscopy, and traditional labeled electron microscopy could reduce some of the conjecture. The cellular physiology of these organisms needs to be elucidated, including the nucleic acid genome and the mechanism that these organisms can use to synthesize biologic components and external apatite structure within such a small volume. Applying modern techniques of genomics and proteomics ***(139)*** should greatly facilitate an understanding of the structure-function mysteries of, NB. This work

should be completed from a microbiology science standpoint, irrespective of any medical implications of the evaluations.

Second, regarding NB, Koch's postulates are not fully satisfied. There is not direct evidence at present that NB are human pathogens, only some circumstantial evidence. Koch's, or Henle-Koch's postulates, are four criteria designed to establish a causal relationship between a causative microbial organism and a clinical disease. The postulates were formulated by Robert Koch and Friedrich Loeffler between 1984 and 1890, associated with attempts to determine the etiology of anthrax and tuberculosis ***(140)***. Koch's postulates are as follows:

1. The organism must be found in all animals suffering from the disease but not in healthy animals.
2. The organism must be isolated from a diseased animal and grown in pure culture.
3. The cultured organism should cause disease when introduced into a healthy animal.
4. The organism must be re-isolated from the experimentally infected animal.

Modern microbiology, especially virology, has shown that microbial agents can indeed be human and animal pathogens, without satisfying all of Koch's postulates, attributable, for instance, to the presence of the asymptomatic carrier and the ability of some individuals to resist disease even when the pathogen is introduced directly into the organism. However, if the medical and microbiological communities are to take NB seriously as a potential pathogen, then targeted research directed at satisfying some of Koch's postulates should be instituted. Supplemental research to define the potential infectious nature, reproductive mechanism and pathogenic properties will also be necessary.

The model for modern infectious disease research is to use parallel approaches to efficiently identify risks to human health. Thus, parallel studies of NB biology, NB-association with disease tissue, causality studies in animals, and screening the potential diseases for this unusual agent are in keeping with this philosophy.

This recommended research schema has a very important potential for early diagnosis and treatment of prostatitis, BPH, and other prostatic and genitourinary disease if NB infection is involved in the pathogenesis. This is because 1) There are now tools for the diagnosis of nanobacterial infection by using NB-specific monoclonal antibodies (ELISA, quick detection kits), and culture methods ***(137)***. 2) There are means of effectively inhibiting NB multiplication by using multi-drug antibiotics, decalcification regimens, and complimentary chemotherapeutics/nutraceuticals ***(136,137,141,142)***.

If, after all of these preliminary investigations, there is still substantial evidence that NB can be implicated in pathogenesis of GU diseases, then a multicenter, randomized, double-blinded, placebo-controlled study of patients with BPH, CPPS, and urinary lithiasis should be conducted with comET as the intervention, to determine if reducing the presence of the purported etiological infection can influence the symptoms associated with and the progression of these common GU maladies.

8 Conclusion

This chapter has evaluated the evidence associated with a potential new infectious agent of the human genitourinary system, nanobacteria. The term nanobacteria may not be the optimal term for these entities and the use of an alternative term, such as CNPs, may be more appropriate until a clear-cut taxonomy is identified. If these ultramicroscopic particles are truly infectious organisms/entities, then their significance to terrestrial processes is potentially quite extensive and profound. Calcifying nanoparticles could be influencing many processes currently assumed to be totally due by inorganic chemical reactions, such as clay mineral formation and dolomite precipitation, as well as other environmental reactions which affect industrial processes ***(54)***. NB/CNP could also be influencing numerous biological processes, for example, formation of biogenic apatite in shells, bones, teeth, calculi, and arterial plaque.

If living entities, these pleimorphic, nanometer-sized self-replicating organisms seem to exist in nature as extremophiles, and have developed an elaborate defense system against environmental attack, namely an apatite shell. There seems to be mounting evidence for the presence of these organisms in human tissues, especially in the genitourinary and vascular systems. There is also evidence that therapies, apparently targeted at NB/CNP defenses, namely chelation or bisphosphonate treatment, in combination with antibiotics known to be cidal to NB/CNP, produce clinical improvement in some patients with symptomatic GU and vascular diseases.

However, there is not strong evidence at present that NB/CNP are indeed human pathogens and can in fact cause disease in humans or any other species. The mere presence of an organism in the site of a diseased organ does not imply cause and effect ***(143)***. Most of Koch's postulates must be satisfied, if NB/CNP are to be labeled as uropathogens. Time will tell if NB prove to be parasitic or saprophytic colonizers of humans, or if they, like *Heliobacter pylori* before them, are shown to be unrecognized infectious agents which produce disease that was previously attributed to non-infectious processes. In the meantime, NB/CNP are very interesting entities, deserving of a targeted human research effort.

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Chapter 18
Strategies for Increasing the Understanding of Chronic Prostatitis/Chronic Pelvic Pain Syndrome

John W. Kusek and Leroy M. Nyberg

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Summary During the past decade, there has been a resurgence in prostatitis research, most notably focused on chronic prostatitis/chronic pelvic pain syndrome. This work included epidemiological studies, evaluation of diagnostic tests, studies of the impact on quality of life and medical costs, pathogenic mechanisms, biomarkers, as well as randomized clinical trials. Despite this effort our understanding of this burdensome and enigmatic condition remains incomplete and management of patients challenging. The etiology of prostatitis/chronic pelvic pain syndrome is not known, risk factors have not been well described, the pathogenic mechanism(s) are obscure, and optimal treatment strategies have not yet been identified. If advances are to be made in the coming years, then the greatest payoff may come from a concerted effort to identify the cause(s) and risk factors for this condition and to develop and validate accurate phenotypes of those with the syndrome. With this knowledge, rationale selection of potential therapeutic agents may be possible to evaluate in well-designed randomized clinical trials.

Keywords Prostatitis; chronic prostatitis/chronic pelvic pain syndrome; male pelvic pain; pain; male urologic health; NIH-Chronic Prostatitis Symptom Index.

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1 Introduction

During the past 10 yr, there has been a substantial increase in the number of published research reports on chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), including epidemiological studies, etiologic investigations, effects on quality of life and health care costs, utility of diagnostic tests, as well as randomized clinical trials. The relationship between prostatitis and other urologic conditions and diseases, including prostate cancer and benign prostatic hyperplasia (BPH), also has been of interest. The catalyst for this resurgence in research interest can be attributed in part to the deliberations of a National Institutes of Health (NIH) sponsored meeting on prostatitis held in December 1995. That meeting was the first time that a group of physicians, basic scientists, epidemiologists, behavioral scientists, patient advocates, patients, and others met, under the sponsorship of the NIH, to identify the gaps in the current knowledge of what was believed to be a common condition. One immediate result of that workshop was a new definition and classification system for the various disorders which fell under the rubric of prostatitis ***(1)*** as shown in Table 1. The consensus was that category III (known as CP/CPPS) is the most common. Another outcome of that meeting was the first allocation of substantial funding by the NIH to research in prostatitis through the establishment of the Chronic Prostatitis Collaborative Research Network (CPCRN). After more than a decade of clinical, epidemiological and basic research it is now time to ask "What have we learned that has improved the care and management of men with CP/CPPS and what have we yet to learn?" This chapter briefly reviews advances that have been made in our understanding of the burden, impact, etiology, risk factors, and treatment of CP/CPPS, and those areas of research that remain unresolved. Suggestions are made for areas that require additional research. The reader is referred to more in depth reviews of many of these issues in recent publications ***(2–7)***.

2 Development of a Symptom Index

One of the first work products of the CPCRN was the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI). This instrument was developed to assess the symptoms and quality of life of men with CP/CPPS ***(8)***. Worldwide adoption

Table 1 NIH Prostatitis Classification Scheme

Category I	Acute bacterial prostatitis
Category II	Chronic bacterial prostatitis
Category III	Chronic prostatitis/chronic pelvic pain syndrome
Subgroups:	
Category IIIA	Inflammatory
Category IIIB	Noninflammatory
Category IV	Asymptomatic prostatitis

of the NIH-CPSI is evidenced by its translation into a large number of languages ***(9–16)***. This has facilitated and standardized prostatitis-related clinical research throughout the world. Importantly, the NIH-CPSI has been found to be valid and responsive ***(17,18)***, the latter attribute critical for use of this instrument as an outcome measure in studies to evaluate treatment effect. The NIH-CPSI has been used internationally as an outcome measure in many randomized clinical trials and as a tool to estimate the prevalence and incidence of prostatitis-like symptoms in a wide range of populations. There is little doubt that this widely adopted tool has become a critical component of CP/CPPS clinical research. Given the fact that the hallmark of CP/CPPS is self-reported symptoms, this instrument will likely remain a key fixture in many of the future clinical research studies for this condition globally.

3 Burden

The health care burden of prostatitis in the United States has been starkly highlighted by the Urologic Diseases in America project ***(19)***. In 1992, approximately 2.2 million physician office visits (age-adjusted rate of 2,477 per 100,000) for prostatitis occurred in the United States, decreasing to approximately 1.8 million (age-adjusted rate of 1,867 per 100,000) in 2000. The overwhelming majority of these visits were believed to be for CP/CPPS. This finding represents cases severe enough to result in a physician encounter. A number of epidemiological studies have been conducted worldwide to assess the prevalence of CP/CPPS, resulting in a better understanding of the real impact of this condition. Many of these surveys have used the NIH-CPSI as a means to estimate disease burden. Sampled populations include urology outpatient practices ***(20,21)***, health maintenance organizations ***(22)***, and the general population ***(23–25)***. The prevalence estimates of CP/CPPS vary substantially when urology practices have been surveyed. For example, the prevalence in outpatient practices was 2.7% in Canada ***(21)*** and 12.8% in Italy ***(20)***. Whether these differences represent true variation in prevalence in the population or are the result of differences in practice patterns, nonuniformity in case ascertainment, or other methodology related factors is unknown. Moreover, these surveys typically include a large number of men who have displayed symptoms long-term and perhaps only represent the "tip of the iceberg" in terms of the population burden of CP/CPPS. Population-based studies have yielded estimates of prevalence of prostatitis-like symptoms of 4.9% in Japanese men ***(25)***, 2.2% in white residents of Olmsted County, Minnesota ***(24)***, 6.0% in Korean men undergoing a military medical examination ***(26)***, 9.7% in Canada ***(23)***, and a lifetime prevalence of 14.2% in Finnish men ***(27)***. Given the shortcomings in methodology of several of these studies, including low response rate and substantial variation in sample selection, it is uncertain whether these population prevalence differences are real. Multinational studies using similar population sampling schemes and uniform validated methods to identify cases of CP/CPPS may provide insights into variation in prevalence as well possible risk factors. Efforts to estimate the incidence of CP/CPPS has been much

more limited. Among enrollees in a health maintenance organization ***(28)***, the incidence of physician-diagnosed CP/CPPS was 2.8 per 1000 person years. The incidence of CP/CPPS in the general population is not known. As stated previously, many of the prevalence surveys have relied on assessing prostatitis-like symptoms by means of the NIH-CPSI. This approach was called into question by one study ***(29)***, which found low agreement between the identification of men with pain symptomatic of prostatitis measured by the NIH-CPSI and self-reported physician diagnosed prostatitis. Further insight on accuracy of case ascertainment by this instrument is provided by a Malaysian study ***(30)***; 65% of men identified in the community as having prostatitis-like symptoms determined by the NIH-CPSI were found to have clinical criteria consistent with chronic prostatitis. These findings are not surprising, because this instrument was not designed to diagnose CP/CPPS; thus, the significance of identifying men in the population with prostatitis-like symptoms and their relationship to actual cases of the syndrome needs to be elucidated. Future effort should be focused on determining the incidence of CP/CPPS (and risk factors) in a population-based sample with inclusion of appropriate racial and ethnic groups. Information on a wide range of urological symptoms, including CP/CPPS, is beginning to emerge from a population-based, racially/ethnically diverse study, the Boston Area Community Health (BACH) Survey ***(31)***. Researchers of such studies will need to use methods to validate cases of CP/CPPS.

Additional measures of disease burden include impact on quality of life and economic expenses associated with CP/CPPS. The negative impact of CP/CPPS on quality of life is substantial and well documented ***(32,33,34)***. A factor that strongly influences quality of life in men with CP/CPPS is sexual function ***(35)***. Studies have documented high rates of sexual dysfunction in men with urogenital pain ***(36,37)*** as well as men with confirmed CP/CPPS ***(38,39)***. The impact of CP/CPPS on the partners of men with CP/CPPS has been infrequently studied ***(39)*** and would offer additional insight into the burden of this condition. Moreover, development of a condition-specific measure of quality of life for CP/CPPS may be useful.

The economic impact of CP/CPPS is substantial, at least in the United States. Among a subset of the CPCRN Cohort Study participants, the annual total health costs were estimated at nearly $4000 with the quality of life subscale of the NIH-CPSI being a predictor of resource consumption ***(40)***. Further work by Turner et al. ***(41)*** among health maintenance enrollees found that healthcare costs were increased in men with CPPS compared with control patients, with the excess costs associated with care for medical problems other than prostatitis. Although such studies are informative future investigations are necessary to determine the impact of effective therapies on reducing overall and prostatitis-specific health care costs.

4 Natural History and Prognosis

Few studies have examined the treated natural history of CP/CPPS. Among nearly 300 men with longstanding CP/CPPS (mean of 6.8 yr since diagnosis) recruited from tertiary care centers and followed for 2 yr in the CPCRN Cohort Study ***(42)***,

45% reported they were markedly or moderately improved on the Global Response Assessment. Importantly, there was no evidence of clinically significant progression of symptoms. These investigators, however, failed to identify baseline demographic or clinical factors which predicted improvement. A unique study by Turner et al. ***(43)*** found that men with a first lifetime episode of prostatitis/pelvic pain syndrome had better outcomes compared with men with a recurrent episode, suggesting that as this condition becomes chronic it becomes less responsive to treatment or is less likely to undergo spontaneous remission. Their finding is consistent with an observation by Nickel et al. ***(44)*** that about one-third of men with prostatitis-like symptoms identified in the community did not report these symptoms after a year of follow-up. The results of several clinical trials have also suggested that newly diagnosed and/or treatment naïve (to the drug being tested) CP/CPPS patients may have a more favorable outcome (i.e., were more responsive to therapy) ***(45,46)***. Future clinical epidemiological studies are necessary to better define the natural history of newly diagnosed cases of CP/CPPS. This information will be useful for physicians counseling their patients on the long-term prognosis of this condition.

5 Risk Factors for and Etiology of CP/CPPS

A substantial body of information has accumulated in the search for an infectious cause of CP/CPPS ***(47–53)***, whereas there has been considerably less emphasis placed on a broader assessment of potential risk factors for this condition. The evidence to date has suggested that it is unlikely that an infectious agent may be the cause of CP/CPPS although further work in this area is necessary ***(54)***. Moreover, there is also no consensus on what factors might predispose men to developing this condition. A recent case-control study ***(55)*** of men enrolled in the CPCRN Cohort Study identified a large number of medical conditions which were more common among cases than in age-matched controls, most notably a previous self-reported history of cardiovascular disease and of neurological disease. In contrast, cases did not report a history of gonorrheal, trichomonal, and genital herpes infections more frequently than controls. The latter observation is consistent with the essentially negative findings from a number of laboratory based studies searching for an infectious cause of CP/CPPS ***(47–53)***. However, a recent study ***(56)*** has demonstrated that *Escherichia coli* strains that cause acute prostatitis are more likely to form biofilms, become resistant to antimicrobials, and persist in the prostate. The implications of these observations for CP/CPPS have yet to be determined. All of these findings are at odds with the common clinical practice of prescribing antibiotics as first-line therapy to treat this condition. Studies have also been conducted to search for noninfectious causes and/or risk factors for CP/CPPS. Ku et al. ***(57)*** examined environmental factors, including duration of sunlight (reduced risk of CP/CPPS) and temperature, but their significance remains unclear. Stress has recently been shown to be a predictor of pain and disability in men with CP/CPPS ***(58)***. It is clear that further work needs to be performed on possible non-infectious risk factors and causes. Long-term

epidemiological studies of high risk (yet to be defined) males may be necessary in order to conclusively identify causative agent(s) and risk factors. It is beyond the scope of this chapter to address our current understanding of the possible pathogenic mechanisms of CP/CPPS ***(59)***. Suffice it to say that the inability to identify causative agent(s) has hampered efforts in this line of investigation.

6 Risk of Other Urologic Diseases in Men With CP/CPPS

Understandably, there is considerable concern among CP/CPPS patients whether this condition predisposes them to prostate cancer. Recent evidence from a white population suggests an episode of acute prostatitis may increase the risk of prostate cancer ***(60)*** but not chronic pelvic pain syndrome. A recent report from the, U.S. Flint Men's Health Study ***(61)*** reported an increased risk of prostate cancer in black men with a history of prostatitis but did not subcategorize the risk in men who had chronic pelvic pain syndrome. Thus, there is only scant information on the importance of prostatitis as a potential risk factor for prostate cancer. Whether prostatitis predisposes men to non-malignant urologic conditions, including BPH and lower urinary tract symptoms has also been little studied. In the Health Professionals Follow-up Study ***(62)*** men reporting a history of BPH had a 7.7-fold greater odds of a history of prostatitis whereas men with moderate or severe lower urinary tract symptoms had a 1.8- and 2.8-fold greater odds, respectively. Much work remains to be done on delineating the relationship, if any, between prostatitis (and CP/CPPS) and the risk of prostate cancer as well as lower urinary tract symptoms.

7 Defining the Phenotype

Given the broad and essentially exclusion-based definition of CPPS, it is likely but not proven that the cause(s) of this condition are likely to be multiple. How to better characterize these men and subset them to tailor their treatment regimen should be a long-term goal. Some effort has been targeted at better defining the phenotype of this condition. Studies have focused on pain sensitization ***(63)***, musculoskeletal dysfunction ***(64)***, toe-spreading ability ***(65)***, sensitivity to intravesical potassium chloride ***(66,67)***, presence of antiproliferative factor, heparin-binding epidermal growth factor-like growth factor and epidermal growth factor ***(68)***, and cytokines and chemokines ***(69–71)*** as means by which patients with CP/CPPS could be better described. There have been recent suggestions that the phenotypes of all the chronic pelvic pain syndromes should be re-ordered focusing on the characteristics of the pain ***(72–74)***. The purpose of this effort could allow more accurate classification and phenotyping, thereby hopefully permitting the tailoring of treatment strategies and improve prognostication of outcomes. Much more multi-disciplinary research needs to be done in this area.

8 Diagnosis

The diagnosis of CP/CPPS continues to rely on self-reported symptoms with clinical work-up aimed at excluding other illnesses. Traditionally, the Meares-Stamey 4-glass test ***(75)*** was recommended as the "gold standard" for diagnosis. On a practical level physicians infrequently use this test in the evaluation of patients suspected of having prostatitis ***(76,77)***. A recent study from the CPCRN Cohort Study ***(51)*** found no difference in the rates of localization of bacterial cultures for men with CP/CPPS compared to controls using the 4-glass test, questioning the diagnostic utility of this procedure. Currently, there are no validated diagnostic tests for CP/CPPS. Such a test might be useful in the diagnosis of cases at an early stage, possibly before development of symptoms, with the hope of preventing its occurrence.

9 Treatment

Perhaps no line of investigation for CP/CPPS has as much interest but with such limited success as the search for effective therapies. There is little evidence to support recommendation of a standard therapy for CP/CPPS. The fact that many different treatment modalities have been studied in the past few years (Table 2) illustrates this point. However, alpha blockers and antimicrobial therapy are often prescribed either as initial treatment in men newly diagnosed with CP/CPPS or those naïve to these therapies as well as in men with longstanding symptoms ***(76,78)***, and the practice appears to be international. Recently, the 6th International Consultation on New Developments in Prostate Cancer and Prostate Disease ***(79)*** reviewed and rated the evidence for the effectiveness of a wide range of therapies. Their report is perhaps the most comprehensive, up to date, and objective review of the literature on treatment strategies. Among their recommended therapies only alpha-blocker therapy for newly diagnosed, alpha-blocker naïve patients was rated as having level-one evidence. However, the support for this recommendation appears to be based on a single clinical trial conducted in Malaysia ***(45)***. In that trial a total of 100 men who had

Table 2 Representative List of Therapies Evaluated for CP/CPPS

Antibiomicrobial agents	Alpha-blockers
5 α-reductase inhibitors	COX-2 inhibitors
Anti-inflammatory agents	Prostatic massage
Minimally invasive therapies	Transurethral needle ablation
Biofeedback	Multi-modal therapy
Physical therapy	Saw palmetto
Acupuncture	Quercetin
Physical activity	Electromagnetic therapy
Pudendal nerve modulation	
Neuromodulating agents	
Immunomodulating agents	

not been treated with an alpha blocker before enrollment, 56% of the men responded (a score of 2 or less on the NIH-CPSI quality of life item) to the drug compared with 36% in the placebo group. Importantly, the duration of symptoms of CP/CPPS was not reported and it is not clear whether they could be called "newly diagnosed." The findings from trials of alpha blocker therapy in men with longstanding CP/CPPS have been inconsistent. In a 6-wk trial (duration of symptoms not specified but subjects but report suggest longstanding symptoms) of tamsulosin a greater decrease in the total NIH-CPSI score was observed in the active treatment group compared with placebo ***(80)***. A similar finding was found in a 6-month trial of alfuzosin (mean duration of symptoms in alfuzosin and placebo groups was 9 and 12 yr, respectively) in Finland ***(46)***. In contrast, a two-by-two factorial design clinical trial of alfuzosin and ciprofloxacin ***(81)*** showed no beneficial effect of alpha blocker treated men with longstanding symptoms (mean time since diagnosis for the various treatment groups ranged from 6.3 to 6.7 yr). The uncertainty about the beneficial effects of alpha blocker therapy is evidenced by a recent systematic review which stated that there was insufficient evidence to conclude with certainty that this therapy is effective for type III prostatitis ***(82)***. Currently, the CPCRN is conducting a randomized placebo-controlled clinical trial of alfuzosin in alpha blocker naïve men with relatively short duration of symptoms (2 yr or less) (www.uppcrn.org). Findings from that clinical trial are expected in 2008.

A second commonly prescribed therapy for CP/CPPS is antimicrobial therapy (antibiotics). The evidence to support the use of antibiotics in men with CP/CPPS is even more meager than that for alpha blocker therapy. To our knowledge, there have been no randomized, placebo-controlled clinical trials of antibiotic therapy among been conducted with newly diagnosed CP/CPPS or in men naïve to this treatment. Moreover, we are aware of only a small number of clinical trials that has been conducted in men with longstanding symptoms with disappointing results ***(81,83)***.

The evidence base for optimal treatment of men with CP/CPPS needs to be strengthened considerably. Although during the past several years a wide range of therapies have been evaluated these studies have suffered from a number of shortcomings including lack of a placebo or sham group, insufficient sample size (low statistical power), and use of nonconventional statistical methods to assess change in the outcome measure, among others. Although there is evidence to suggest that men with newly diagnosed or naïve to the therapy under evaluation are more likely to respond to treatment the significance of this finding is uncertain and needs to be pursued further. Rigorously designed and executed double-blind randomized clinical trials of promising therapies based on an understanding of the pathogenic mechanisms and/or etiologic of CP/CPPS are necessary if this situation is to be improved in the coming years.

10 Future Research

Progress has been made during the past decade to better understand the burden and impact of CP/CPPS and to manage patients with this condition however much remains to be known. As shown in Table 3, there are as of yet many unresolved

Table 3 Future Research Emphasis

- Long-term natural history studies among newly diagnosed/treatment naïve subjects to identify etiologic agent(s) and risk factor(s)
- Multi-national population-based surveys to estimate incidence rates
- Validation of the clinical significance of men identified with prostatitis-like symptoms by the NIH-CPSI and other survey methods
- Randomized placebo controlled clinical trials to identify a standard therapy
- Establish clinically and research relevant phenotypes
- Understand the pathogenic mechanism(s)
- Elucidate the relationship between CP/CPPS, prostate cancer, benign prostatic hyperplasia, and lower urinary tract symptoms
- Development of a condition-specific measure of quality of life

questions about the diagnosis, natural history, disease burden, and treatment of men with CP/CPPS. Hopefully, as there has been in the past, government and the private sector in collaboration with patients, their families and respective advocacy groups, will support these needed investigations.

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Chapter 19
Chronic Prostatitis/Chronic Pelvic Pain Syndrome: The Past, Present, and Future

J. Curtis Nickel

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Summary Our understanding of "chronic prostatitis" (CP) has evolved over the last century from being an infectious disease, a condition that was easy to comprehend and simple to treat with antimicrobials to an inflammatory condition that could be managed with anti-inflammatories. Until recently, most still believed that CP involved the prostate and that therapy was prostatocentric. However, our traditional biomedical model has failed most patients. Our understanding of the condition we now call chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) has further evolved to a concept of disease progression in susceptible individuals through a series of initiating events followed by neurological, endocrine, and immunological changes modified by cognitive mechanisms. This new understanding has promoted major shifts in diagnosis and treatment that should improve the management of patients diagnosed with CP/CPPS.

Keywords Prostatitis; research.

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1 The Traditional Concept of Prostatitis

Prostatitis used to be so easy to understand and to so simple to manage. Its very name, "prostat…it is," implied that the problem was in the prostate and was associated with inflammation. Shortly after the turn of the last century, medical researchers and physicians believed that all inflammation was caused by a microbial infection. Significant effort was expended in the attempt to locate, identify, and then eradicate the offending prostate pathogen. In the late 1930s, antibiotics were discovered and, by the mid 1940s, many learned men and women in the medical profession even speculated that infectious diseases, including prostatitis, were going to be relegated to a historical footnote. However, antibiotic therapy for prostatitis turned out to be very disappointing, and, a decade later, a number of researchers even suggested that not all cases of prostatitis may be the result of an infection or, for that matter, even inflammation. In 1968, the localization technique for organisms in the male lower urinary tract was standardized. It soon became very apparent that only about 5–10% of prostatitis cases could be attributed to localization of a uropathogenic bacteria to the prostate. It took the research community another 10 years to come to this realization. In 1978, the traditional classification system for prostatitis was described, a system quickly adopted by the rest of the urological community. It turns out that more than 90% of men presenting to physicians with a prostatitis syndrome would be diagnosed with nonbacterial prostatitis (no infection, but inflammation) and protatodynia (no infection, no inflammation). Almost 20 yr later, it was recognized that in chronic cases of prostatitis, the prostate gland itself may not be actually involved. The presently accepted (but not necessarily accurate) classification system of prostatitis disorders attaches a diagnosis of Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) to almost all the patients previously diagnosed with chronic nonbacterial prostatitis and prostatodynia. This particular book has been written to better understand and management those patients.

2 An Improved Diagnostic Strategy

The urological community has more or less abandoned the traditional 4-glass lower urinary tract localization technique. The much simpler Pre- and Post-Massage Test (PPMT) provides reasonable clinical accuracy in ruling out prostate infection. The differentiation of cases based on the degree of prostate specific inflammation noted in the expressed prostatic fluid or the post-massage specimen has not proven to be clinically relevant. More importantly, we have now realized that we must evaluate more than the prostate and lower urinary tract in our assessment of a CP/CPPS patient. The physical examination, including the mandatory digital rectal examination, must include an evaluation of painful areas including trigger points in the perineum and pelvis, as well as a focal neurological examination. The psychosocial parameters, including depression, anxiety, disability, and psycho/social/sexual interactions, must be explored. The importance of these latter evaluations becomes apparent when we look at future treatment options.

However, the diagnosis of CP/CPPS now depends, once infection, malignancy, and other treatable causes of pelvic pain and voiding symptoms are ruled out, on a descriptive symptom complex. This symptom complex invariably includes pain. The creation and validation of the National Institutes of Health (NIH) Chronic Prostatitis Symptom Index (CPSI) has become the most important diagnostic development available for clinical research (epidemiology, etiology and, in particular, treatment studies) and clinical practice. The NIH-CPSI has allowed us to determine the incidence and prevalence of prostatitis or CP/CPPS-like symptoms in the male population, define patients for etiological investigations, and determine response rates in therapeutic clinical trials. It has become an invaluable tool in clinical practice, not only for the initial diagnostic evaluation, but also for long-term follow-up and assessment of treatment response in individual patients.

3 Has Our Traditional Biomedical Model of Therapy Failed?

Physicians know how to treat infection: with antibiotics. And, for the most part, antibiotic treatment of the bacterial categories of prostatitis is relatively successful. In some cases of CP/CPPS, particularly in early diagnosed, antibiotic-naive CP/CPPS patients, antibiotics also appear to successfully ameliorate symptoms. However, for most patients diagnosed with CP/CPPS, particularly if the patient has had the diagnosis for a long duration and had previously been treated with antibiotics, antibiotic therapy is not very useful. Properly designed, randomized placebo-controlled clinical studies in well-categorized patients show that antibiotics ameliorate symptoms in these patients no better than placebo.

Physicians know how to treat inflammation: with anti-inflammatories. However, at least two well-designed placebo-controlled studies could not confirm sufficient efficacy to lead to a recommendation for anti-inflammatories as a monotherapy for patients with CP/CPPS.

Physicians know how to treat benign prostate disease: with alpha-blockers and 5-alpha reductase inhibitors. The efficacy of these agents, particularly alpha-blockers, is modest at best. Alpha-blockers appear to work better when treatment is continued for long term in alpha-blocker naïve patients with a recent diagnosis. 5-alpha reductase inhibitors appear to work better in older men with large prostates; in other words, those with co-occurring CP/CPPS and benign prostatic hyperplasia.

Similarly, the use of pentosanpolysulfate in some may be beneficial, particularly if they have interstitial cystitis-like symptoms, whereas herbal-based therapies such as quercetin, saw palmetto, and pollen extract show some promise. Minimally invasive surgical therapies have not undergone rigorous evaluation, and surgery will only be successful if a surgical indication is discovered.

It is easy to come to the conclusion that our standard biomedical model of therapy is failing the majority of patients with a long-term diagnosis of CP/CPPS. So then, what does the future hold?

4 Our Understanding of the Etiology of CP/CPPS Is Improving

Infection and inflammation may still be involved in the pathogenesis of CP/CPPS, but as initiators of the process, not the direct cause. Infection (bacterial prostatitis, urinary tract infection, including cystitis, urethritis, sexually transmitted diseases, epididymitis, etc.), inflammation (intraductal reflux of urine immunogens, allergic or auto-immune phenomenon, etc), or trauma (repetitive perineal, surgical or sexual trauma, or muscle/tendon/nerve injury), dysfunctional voiding or some as yet to be defined initiator can trigger a process of local inflammation and neuromuscular damage in some anatomically and/or genetically predisposed men. Peripheral nerve sensitization can occur if the initiator process is not dealt with quickly. If the peripheral event (initiator process) followed by peripheral nervous system response continues, a central neuropathy evolves with central nervous sensitization of spinal neurons. This leads to hyperalgesia (mildly uncomfortable stimuli perceived as painful) and allodynia (normal stimuli perceived as painful).

Through spinal "crosstalk" or "convergence," the pain spreads and can incorporate both somatic and visceral components. This can evolve to pelvic floor dysregulation which leads to further pelvic floor neuromuscular dysfunction and more pain. The central neuropathic state is further modulated by higher central nervous centers that control depression, anxiety and coping which are more likely to be a maladaptive central mechanism. Is it any wonder that treating the peripheral event in someone who has been suffering from the condition for months or even years, results in such poor response?

5 The Evolution of CP/CPPS Treatment

Our understanding of the condition we call CP/CPPS has undergone significant changes since we have accepted the fact that treating prostate infection and inflammation is not the key for most patients with this diagnosis. That being said, we must still first deal with the initiators (infection, inflammation, trauma, dysfunctional voiding etc) or else our therapy for the chronic immune, neurologic and muscular dysfunction may fail. In the future we hopefully will be able to identify which of these factors are important in the genesis and persistence of the individual patient's symptoms. And that may be the key; patients with CP/CPPS are not a homogenous group. Clearly, patients have different immune, neurologic, and muscular disturbances as well as central coping mechanisms that predict all patients will not respond identically to a simple single treatment modality. In the future, patients will be further categorized according to more accurate history, more rigorous physical examination, better localization tests and, hopefully, by specific biomarkers. The treatment, then, will be tailored to the specific dysfunction(s) identified in each individual patient.

5.1 Immunomodulation

Some patients with CP/CPPS (likely a minority) clearly have an immune system disorder (either allergic or autoimmune) that may benefit from specific immunomodulatory (e.g., anti-cytokine) therapy, either as a monotherapy or part of a multi-modal therapeutic algorithm. Such a trial is currently underway for the specific chronic pelvic pain of interstitial cystitis.

5.2 Neuromodulation

Neuromodulation will be the key for the majority of patients suffering from long-term chronic pelvic floor neuropathy with central sensitization. In fact, we are already evaluating tricyclic antidepressants and pregabalin in clinical trials. Newer agents or minimally invasive neuromodulatory therapies (e.g., percutaneous sacral nerve stimulation) may hold promise for the future.

5.3 Physical Therapy

Pelvic and perineal muscle spasm, associated tendinous/ligamentous injuries, and specific trigger points can be identified in many patients with CP/CPPS. These areas can be localized and treated employing physiotherapeutic techniques proven successful for other muscular dysfunction pain syndromes elsewhere in the body. These techniques would include heat application, injection therapy, trigger point release, acupressure, acupuncture, and massage therapy. Many of these techniques are presently being evaluated.

5.4 Cognitive-Behavioral Therapy (CBT)

CBT has been used successfully in other chronic pain conditions, such as chronic back pain. Recent comprehensive biopsychosocial studies in CP/CPPS populations have shown that the psychosocial parameters that influence pain and disability in CP/CPPS patients are different, but all potentially treatable. CBT is currently being evaluated for CP/CPPS patients with goal of not necessarily decreasing the pain, but improving pain coping, pain perception, and thereby improving quality of life and decreasing disability.

5.5 Other Exciting Therapeutic Developments

Herbal therapies hold promise in alleviating symptoms in CP/CPPS patients and should be further evaluated. Focused heat therapy, such as transurethral microwave

thermotherapy, has shown promise, but the technique of applying local heat to the prostate/pelvic floor area has never been developed. New research is identifying specific gene patterns in some patients with CP/CPPS and in the future, specific gene therapy may be possible. As our understanding of this condition improves, so will our therapeutic options.

6 The Future

The future must be built on the past. Our successes will depend on the dedicated researchers of the distant and recent past who have rigorously studied the condition and tested multiple therapeutic possibilities. The improvement of our management of the future CP/CPPS patients now lies in the hands of the basic scientists, clinical researchers and dedicated clinicians who have committed themselves to improving our understanding and treatment of this enigmatic chronic pain condition.

Chapter 20
Therapy for Category III Prostatitis: A Synthesis

Daniel A. Shoskes

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2 CPPS Is a Syndrome, Not a Disease 266
3 Duration and Chronicity of CPPS Should Influence Approach 266
4 Evidence-Based Medicine and CPPS: Strengths and Limitations 267
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6 The Patient with Long Duration and Recalcitrant Symptoms 270

Keywords prostatitis, pelvic pain, therapy, research, antibiotics, phytotherapy

1 Introduction

> "Do not fear to be eccentric in opinion, for every opinion now accepted was once eccentric."—Bertrand Russell

As the authors of the preceding chapters have ably documented, the prostatitis syndromes are common, poorly understood, and have a significant impact on quality of life. There is limited evidence based medicine published to guide therapy, especially for category III/chronic pelvic pain syndrome (CPPS). In the preceding chapter, Dr. Nickel has outlined the limitations of the biomedical model for therapy of CPPS and laid out areas for further research that may yield promising new ways to divide patients by etiology and to direct therapy. Nevertheless, in clinical practice patients and their physicians need therapy now, despite the limitations of the evidence. In this chapter, I would like to give my own approach to therapy, using a combination of evidence based medicine and clinical experience.

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2 CPPS Is a Syndrome, Not a Disease

In the absence of reliable biomarkers and diagnostic tests, CPPS remains a syndrome, populated by patients with diverse etiologies who will respond to different therapies. Nothing has humbled me more than over ten years of treating this condition than my complete lack of ability to predict, based on initial evaluation, which patient will end up responding to which class or combination of therapies. I also continue to find patients managed long term for chronic prostatitis who are eventually diagnosed with a different urologic disorder (e.g., stones, strictures, cancer) that may have been present from the start or that may have developed subsequent to the prostatitis. Despite the current limitations for validated tests and therapies, we do owe every patient an appropriate history and physical to ensure that there is no other cause for their symptoms.

3 Duration and Chronicity of CPPS Should Influence Approach

Although we cannot yet differentiate patients with objective parameters, two clinical patterns present themselves. The first is the early, relatively treatment-naive patient, more commonly seen by primary care physicians than by urologists. The second is the late chronic patient who may have had symptoms for years and whose response to therapy is minimal or short lived. The early patients are more likely to have the most diverse etiologies, by virtue of not being self selected by treatment response. Their pain and urinary frequency could be the result of anything from urethritis to cystitis, sexually transmitted diseases, stones, hernias, interstitial cystitis, overactive bladder, trauma, and anything in between. These patients are most likely to respond to monotherapy targeted at the underlying etiology and therefore removal of the instigating cause often leads to complete resolution of symptoms. It is in these early patients that cultures are the most meaningful.

By contrast, late patients who are recalcitrant to therapy may have the greatest similarities. These patients often have multifactorial symptoms that may have been instigated by an initial infection but whose components may now include autonomous inflammation, tissue injury, dysfunctional voiding, muscle spasm, and maladaptive physical, neurological, and psychogenic responses. In these patients, monotherapy is less likely to be effective and, indeed, removing the initial instigating factor may have little effect on symptoms. Cultures in these patients are less likely to uncover a pathogen (fewer than 7% will have uropathogens localized to the prostatic fluid, a number similar to asymptomatic controls). Indeed, the primary function of cultures in these patients in my experience is to help convince patients that they do not have an ongoing infection and to persuade them to try therapy other than antibiotics. These are the patients that often have the long term label of “prostatitis” in whom other new diagnoses need always to be considered and not just attributed to another flare up.

4 Evidence-Based Medicine and CPPS: Strengths and Limitations

As outlined in this book, the past ten years has seen great strides in CPPS research. We now have a syndrome based classification, a validated symptom score, and guidance for therapy based on prospective randomized placebo controlled studies. We also have novel therapies supported by small preliminary studies that await larger scale verification. However, this wealth of evidence does have limitations for the practical care of patients. Unfortunately, we have a better idea of what doesn't work than what does. Studies done at tertiary referral academic centers have attracted participants that, by definition are more complex and likely to have failed multiple previous therapies. Additionally, studies to date have primarily focused on monotherapy which, as mentioned previously, may be inadequate for the complex chronic patient. Indeed, to adequately power a study of multimodal therapy requires a very large (and often impractical) number of patients, especially if subset analysis of the value of each therapy alone is planned. Therefore, with scientific evidence in hand, the clinician today needs a combination of science and art in the approach to CPPS patients.

As we have explored in this book and as summarized in Figure 1, there are multiple inter-related pathways that contribute to the symptoms of CPPS. For the advanced patient, all pathways may be simultaneously working; therefore, multimodal therapy would seem to have the best chance at stopping the vicious cycle. Figure 2 shows how several of the therapies discussed in previous chapters may fit into this scheme. This list is not exhaustive, and some therapies may work in ways not yet fully elucidated. For instance, the tricyclic antidepressants may also reduce inflammation by blocking mast cells, pelvic massage may also reduce stress and bioflavonoids may inhibit the growth of several different micro-organisms.

5 The Early "Treatment-Naive" Patient

As Dr. Egerdie discussed, all randomized placebo controlled trials of antibiotics in CPPS show no benefit. These studies, however, often did not include early treatment naive patients and we know from clinical experience that many if not most of these patients will have their symptoms resolve after antibiotics. Clearly, urinary tract infections need to be treated with antibiotics, either for 1–2 wk (urethritis, cystitis) or 4–6 wk (category II prostatitis). For the 7% of CPPS patients who do have positive expressed prostatic secretion cultures, the benefit of antibiotics to improve symptoms is unclear. Nevertheless, for the true first time treatment naive patient, I think it would be a mistake to withhold a course of antibiotics, based only on data from long term patients. If, after 4–6 wk of therapy, there is no symptomatic response despite a bacteriologic response, then further courses of antibiotics are unwarranted in this setting.

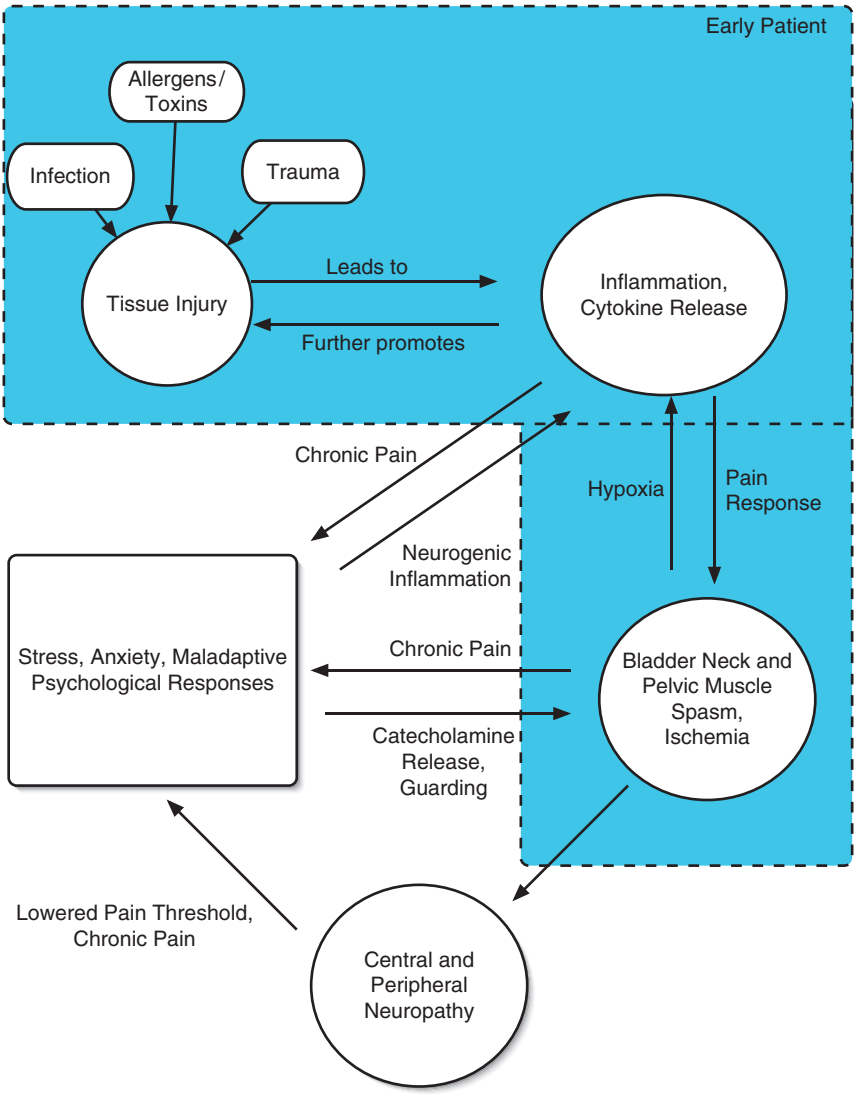

Fig. 1 Proposed schematic diagram of potential etiologies for CPPS. the shaded area encompasses likely pathways for the early, treatment naive patient. The long term patient may have contributions from every pathway

If antibiotics are not effective, it is reasonable to treat next with an alpha blocker. Dr. Krieger has reviewed the evidence to date and we should expect to see the results from a large NIH placebo controlled study of alfusozin in treatment naive patients by 2008. Both tamsulosin and alfusozin seem equally effective; however, in my experience, younger men seem to tolerate alfusozin better, because the retrograde ejaculation that can be associated with tamsulosin is more troublesome in

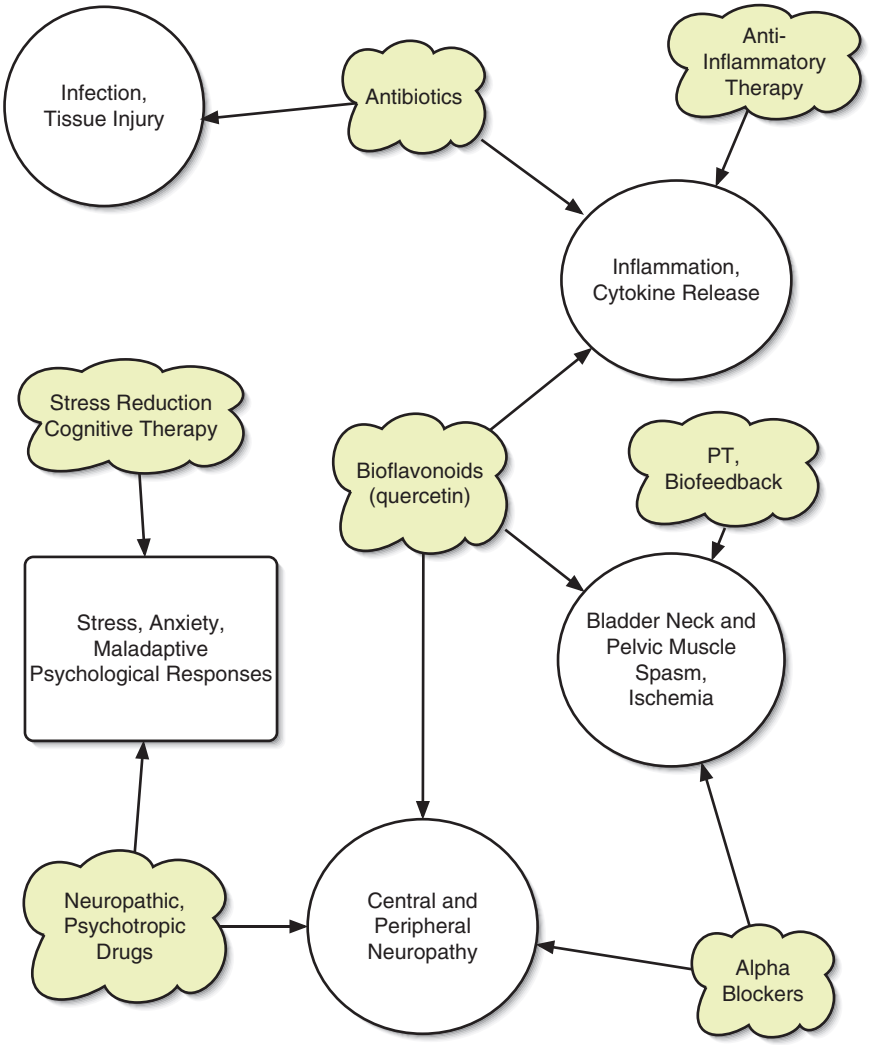

Fig. 2 Proposed modes of action of therapies for chronic pelvic pain syndrome. PT, physical therapy

these men. It is important to realize that alpha blockers may require up to 3 months to achieve their maximal benefit in CPPS and that patients do not necessarily have to suffer from lower urinary tract infections to benefit from alpha blockers.

Another option is phytotherapy. As discussed in my previous chapter, the bioflavonoid quercetin has multiple potential beneficial effects in patients with CPPS. It is anti-inflammatory and reduces white count and oxidative stress in prostate fluid. It is an antioxidant and may help with ischemic muscles undergoing anaerobic

metabolism. It is also neuroprotective in several models of nerve injury and damage. I use 500 mg of quercetin two to three times per day, preferably combined with bromelain and papain which may enhance absorption (Prosta-Q; Farr Labs, Santa Monica, CA). Alternatively, I will use a preparation that combines quercetin with the other phytotherapy documented to be of value in these patients, bee pollen (Q-Urol; Farr Labs), starting at one capsule twice a day. Many patients notice an improvement in the first week; however, it may take up to 6 wk to have an effect.

6 The Patient with Long Duration and Recalcitrant Symptoms

CPPS patients with symptoms dating back years and minimal or intermittent response to therapy requires evaluation and therapy that addresses all the potential pathways in Figure 1. Treatment selection will be based both on the evaluation and on response to previous therapies. It is worth doing a set of cultures and a course of antibiotic therapy if it has not been tried before, but in these patients that is unlikely. Nevertheless, I will occasionally see a patient who has failed months of quinolone therapy without cultures who grow out *Escherichia coli* resistant to ciprofloxacin and benefited from sensitivity-directed antibiotic therapy. One therapy proposed for CPPS patients who do not respond to antibiotics alone is combination with repetitive prostate massage, a therapy that predates antibiotics. In my experience, this combination is effective in the relatively small subset of patients who either have significant symptom relief after the first diagnostic prostate massage or in those patients with high-volume, purulent prostatic secretions. In the former group, it may be that the prostate massage is also providing massage of pelvic muscle spasm. In the latter group, massage may be releasing infected prostatic secretions trapped within obstructed ducts that do not clear with ejaculation.

Supportive measures are important to emphasize in patients with recalcitrant CPPS. These include sitz baths, the use of a donut-shaped cushion during prolonged sitting, use of modified bicycle seats, and the search for and avoidance of food triggers. Common food triggers include caffeine, spicy foods, and alcohol. Other patients may have a ensitivity to acidic foods or to foods containing wheat (gluten).

My first step beyond antibiotics is a combination aimed at inflammation and smooth muscle spasm. I will usually begin with alfusozin 10 mg per day and quercetin/bee pollen (Q-Urol) twice a day for 6–12 wk. For patients who have documented pelvic muscle spasm, especially if associated with trigger points, I will refer to our pelvic physical therapists. Unfortunately, there are not many centers with the luxury of having therapists with specialized pelvic muscle training and general "pelvic" regimens such as Kegel exercises may not be helpful or may even be harmful. The benefit of this specialized pelvic therapy is as yet unproven, and the National Institutes of Health is in the midst of a pilot study to see whether multicenter prospective trials with a reasonable sham control group are feasible. If pelvic

physical therapy is not feasible, helpful or if trigger points are not detected, an alternative is neurotropic agents, as discussed by Dr. Pontari. I will usually start with nortriptyline or amitriptyline, beginning at a low dose (10 mg at bedtime for either) with gradual escalation. If these don't help, I will try gabalin or pre-gabalin. A National Institutes of Health randomized placebo-controlled trial or pre-gabalin should be completed in 2008, giving more information on the efficacy of this approach. Finally, for patients with persistent pain despite these interventions, I will refer to pain management for consideration of therapies discussed by Dr. Mekhail.

For other therapies with anecdotal evidence of success, I think it is important to weigh the risk-reward ratio. Transurethral resection of the prostate for pain is unlikely to help and may worsen symptoms. On the other hand, therapies such as acupuncture, Permixon and medical therapy for prostatic calcifications (EDTA plus tetracycline) are unlikely to harm and may help. I have not found pentosan polysulfate to be of value in the empiric therapy of CPPS and it's empiric use can be limited by side effects and the long duration required to see a response. Whether the cognitive behavioral therapies utilized in other pain syndromes has a role in CPPS remains to be proven.

Ultimately, patients should be encouraged that most will ultimately improve. Although long-term epidemiologic studies are lacking, if most patients who develop CPPS at a median age of 42 did not get better, we would be seeing a large population of men in their seventies who have suffered constantly for more than 30 years, and this has not be my experience. The therapies outlined in this chapter and discussed in depth in this book can help the majority of patients, even those with long histories of recalcitrant symptoms. For the remainder, the future as discussed by Dr. Nickel should hold hope.

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